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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.01/A1

Topic: A.02. Postnatal Neurogenesis

Support: NSERC
CIHR
MSFHR

Title: Adult-born neurons are structurally plastic and remain morphologically distinct from developmentally-born neurons

Authors: *J. S. SNYDER, D. ESPINUEVA, T. O'LEARY, S. P. CAHILL, D. SEIB, J. D. COLE

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Abstract: While new neurons are continuously added postnatally in the dentate gyrus of the hippocampus, only a fraction survive to integrate into the existing neural circuitry. Hippocampal-dependent learning during modulates the survival and integration of adult-born neurons. However, little is known about learning-induced plasticity across stages of maturity, and whether developmentally-born neurons display experience-dependent plasticity. The present study therefore examined the effects of single-day intensive water maze training on dendritic, axonal, and spine morphology in rat retrovirally-labelled granule cells, birth-dated at either postnatal day 1, or in adulthood at 1, 3, or 6 weeks prior to testing. Learning had no effect on total dendritic length or total spine density. However, training did increase mushroom spine densities in 1 and 6-week-old adult-born cells. Spatial learning also altered spine distribution across the molecular layer; while adult-born cells displayed greater spine density in the outer two-thirds of the molecular layer, which receive inputs from the entorhinal cortex, learning reduced the regional disparity. Interestingly, 7-week-old adult-born cells were morphologically distinct from developmentally-born cells, displaying shorter dendritic length and greater spine densities. These differences could be due to immaturity of the adult-born cells or the fact that they were born in adulthood and not early postnatal development. To distinguish these possibilities, we injected retrovirus into adult rats and examined cells 8 and 24 weeks later. Here we find that the increased spine density in adult-born cells persists at 24 weeks of age. Moreover, 24-week-old adult-born cells having significantly more mushroom spines than younger adult-born cells and developmentally-born cells. Continued analyses of dendritic length and complexity, as well as presynaptic terminal frequency, size, and morphology will further our understanding of the plastic potential of granule cells across stages of maturity. Collectively, our data suggest that adult-born granule cells exhibit learning-induced plasticity at specific cell ages. Moreover,

structural differences between developmentally-born cells old adult-born cells suggests that adult-born neurons either mature over much longer timescales than previously appreciated, or are a functionally distinct cell type from developmentally-born cells.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.02/A2

Topic: A.02. Postnatal Neurogenesis

Title: Neurogenesis in adult human hippocampus, what signature genes expressions tell us?

Authors: *A. KUMAR^{1,2}, V. PAREEK^{3,2}, H. N. SINGH^{4,2}, S. K. GHOSH^{5,2}, P. KUMAR^{6,2}, M. A. FAIQ^{7,2}, C. KUMARI^{8,2}

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Abstract: Introduction Continued neurogenesis in the adult human hippocampus was currently in question. A study of the expression patterns of specific neurogenesis signature genes respective to the stages of neuronal maturation in developing to adult age hippocampus may provide important insight regarding it. **Materials and Methods** The expression data for the neurogenesis signature genes in post-mortem human brain tissue of the Prenatal (n=15), Infants-Early Childhood (n= 5), Adolescence (n= 6), and Adulthood (n=6) ages from the hippocampus were downloaded from development transcriptome database of Allen Brain Atlas (<http://www.brainspan.org/rnaseq>). Data were analyzed for the differential expression (expressed as the p-values) specific to the neurogenesis maturation stages and graphs were plotted to study the trends. **Results** Sharp decreases in expression of genes for proliferation (Nestin-1.17E-06, SOX2-0.04, SOX4-5.2E-19, GFAP-1.7E-11, Ki-67-0.4E-3, CD24-1.12E-16) and early maturation (PAX6-2E-3, NCAM-1-2E-3, NeuroD-5.5E-3, DCX-2.3E-22, Sema3C-3.13E-11, STMN2-6.54E-9) but increases in late maturation stages (NeuN-0.007, TH-3.4E-7, GAD65/GAD2-4.6E-8, MAP2-0.05E-2) from prenatal to childhood age, thereafter continued decrease in proliferation and early maturation (significant to insignificant), but maintained or slightly increased expression in late maturation stages from childhood to adult age were noted.

The changes in the expressions found least significant when compared between closer postnatal age groups with almost no significant change between teen and adult age. A gain of statistical significance, when compared with the prenatal expression, from childhood to teen or teen to adult age, for some proliferation (Nestin, GFAP, SOX2, and SOX4), and late maturation genes (NeuN, GAD65, CALB1), and an exclusive gain of significance with an increase in expression was noted for late maturation genes between teen and mid-age (NeuN-1.7E-7 to 1.3E-8, GAD65-2.09E-20 to 1.8E-26, CALB1-0.19 to 0.003). **Discussion** The expression patterns of signature genes indicated a post-childhood decrease in proliferation and early maturation but maintained or slightly increased late maturation up to adult age. In general, the expressions of neurogenesis genes get stabilized post-childhood which seems maximum between teen and adult age. A progressive decrease in some proliferation and early maturation but maintained or a significant gain in the expression of late maturation genes between postnatal age groups, especially between teen and mid-age, indicated for the minimal but persistent neurogenesis in adult hippocampus.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

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Program #/Poster #: 029.03/A3

Topic: A.02. Postnatal Neurogenesis

Support: R01 AG054649-01

Title: Origin and migration of postnatally generated hippocampal granule cells throughout life in mice

Authors: ***K. D. MURRAY**¹, Y. JIN², H.-J. CHENG²

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Abstract: In rodents, neurogenesis continues to occur in the hippocampus and subventricular zone throughout adulthood and into old age. In the hippocampus the dentate gyrus (DG) subgranular zone is the neurogenic niche where resident stem cells are localized. Radial glia like cells (RGLCs) give rise to daughter cells that produce newborn hippocampal granule cells (GCs) which functionally integrate into existing hippocampal circuitry. During embryonic cortical development radial glia (RG) cells form a critical scaffold allowing newborn neurons to migrate along their primary process leading to the generation of laminae in an inside out manner. Whether RGLCs in hippocampus play a similar role is unknown. In contrast to neocortex the DG GCs form in an outside in manner and newborn GCs in adult brain tend to migrate away from

their clonal origin suggesting the morphofunctional role of RGLCs in adult hippocampus differs from RG in embryonic cortex. In order to investigate the relationship between adult RGLC stem cells and lamination of DG we utilized the Gli1CR_eER transgenic mouse line in combination with multiplex immunolabeling to determine the developmental origin of adult RGLCs and the migratory path of subsequently generated GC neurons throughout life. In postnatal brain we identified three distinct waves trajectories of RGLC development. In the first month following birth few RGCLs were observed and the number of mature GCs was low. However, from approximately 1 month until 3 months of age we observed a 7-fold increase in RGCL number. During this period the number of intermediate progenitors and newborn GCs also increased in number and maintained a steady rise until approximately 1 year old (y/o). At 1 y/o, however, both RGCL and newborn GC numbers declined rapidly. We also examined the laminar distribution of newborn GCs throughout postnatal development. Contrary to the notion that adult neurogenesis contributes to generalized turnover of GCs throughout life we found that the vast majority (70% on average) of adult-born GCs reside within the inner 1/3 of the DG GC layer while few migrated to the outer most regions. This observation held true even when newborn neurons were examined 1 year later. These observations suggest that (1) adult-born GCs in hippocampus originate from a population of RGCLs activated or generated in postnatal brain and that (2) these adult-born GCs populate a specific laminar region of the DG. The declining population of RGLCs and newborn GCs after 1 year may have implications of the loss of adult-neurogenesis in aged brains.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.04/A4

Topic: A.02. Postnatal Neurogenesis

Support: NIH Diversity Supplement, 3R01NS097271-01

Title: Precise cell cycle regulation of cerebellar granule cell progenitors by insulin-like growth factor 1

Authors: *T. SHAND, H. ZONG
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Abstract: Precise control of the cell cycle is critical for normal development. The counteraction between positive and negative cell cycle regulators ensures the precision. During cerebellar development, the cell cycle of granule cell progenitors (GCPs) is regulated by multiple cell extrinsic factors. Sonic hedgehog (Shh) is a powerful mitogenic factor for GCP proliferation,

while bone morphogenetic proteins (BMPs) block GCP proliferation and promote differentiation. Overactive Shh signaling in GCPs drives the formation of the Shh-subtype of medulloblastoma. While studying medulloblastoma, our lab identified insulin-like growth factor 1 (IGF1) as a critical niche factor for tumor progression, since loss of IGF1R specifically in tumor GCPs resulted in a significant blockade of tumor progression. This prompted us to investigate whether IGF1 signaling is critical for cell cycle progression of normal GCPs. To determine the role of IGF1R signaling in normal GCP development at single-cell resolution *in vivo*, we used a mouse genetic tool called mosaic analysis with double markers (MADM). Using a GNP-specific Cre, MADM generates sporadic GFP⁺ IGF1R KO GCPs and RFP⁺ WT siblings simultaneously. Since RFP⁺ WT cells provide a perfect internal control for GFP⁺ mutant cells, the impact of IGF1R loss on mutant cells can be determined by calculating green-to-red cell ratio in the GCP population. At the conclusion of cerebellar development on postnatal day 21, the G/R ratio was significantly less than one, indicating that IGF1R is a positive regulator of GCP development. We next asked if IGF1R is important for GCP proliferation or survival. We found that IGF1R is necessary for GCP proliferation but had no effect on survival. To further investigate how IGF1 coordinates with Shh and BMP to regulate GCP development, we analyzed the abundance of Shh, IGF1, and BMP during cerebellar development and found the expression level of Shh and IGF1 is high during early development, then gradually decline, while the expression level of BMP followed the opposite trend. Therefore, we hypothesize that while Shh and BMPs counteract each other to promote GCP proliferation and differentiation, respectively, IGF1 serves as a robustness factor. Specifically, high expression of IGF1 during early development prevents premature GCP differentiation, while decreased expression of IGF1 during late development ensures prompt cell cycle exit and differentiation induced by BMPs. We will recapitulate this multi-factor environment *in vitro* and perform IGF1 gain- and loss-of-function experiments *in vivo* to test this hypothesis.

Disclosures: T. Shand: None. H. Zong: None.

Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.05/A5

Topic: A.02. Postnatal Neurogenesis

Title: Exploring *in vitro* neurogenesis of oligodendrocyte progenitor cells from the adult mouse suprachiasmatic nucleus

Authors: *D. H. BELIGALA, A. DE, H. RUFF, E. A. TEPE, M. E. GEUSZ
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Abstract: Studies have reported oligodendrocyte progenitor cells (OPCs) differentiating into neurons in adult brain, but it is unclear how this neurogenesis creates neurons matched to specific brain areas. This study examined in vitro neurogenesis by OPCs derived from the suprachiasmatic nucleus (SCN) of juvenile and adult mice. The SCN contains the major mammalian circadian clock and has many properties of neurogenesis including proteins typical of stem and progenitor cells of the developing brain. An additional issue addressed was whether SCN OPCs are unique in a way that might explain the SCN's apparent immature properties. SCN explants were maintained in serum-free NeuralX medium designed for OPC culture along with fibroblast growth factor-2 (FGF2), platelet-derived growth factor-AA (PDGF-AA), and GS22 supplement. The explants attached to cell culture dishes and produced cells that migrated from the tissue edge and proliferated. Explants were removed after 11 to 25 days in culture. Some OPC cultures were then treated with BrainPhys medium supplemented with SM1 to induce differentiation. We previously used immunocytochemistry to characterize cultures in NeuralX and BrainPhys and identified high percentages of cells positive for OPC markers before differentiation (Olig2, PDGFR- α , NG2) and similarly high numbers of cells positive for markers of mature neurons (NeuN, MAP2), neuroblasts (doublecortin), and immature neurons (TUJ) after differentiation. About 42% of the BrainPhys-treated cells were positive for neuropeptide VIP that is expressed abundantly in the SCN, suggesting local specificity of OPC-derived neuronal cell fate. Microelectrode array (MEA) recordings confirmed that neurons were present. We detected action potentials at 78% of the 60 MEA electrodes, and the number of spikes ranged from 1 to 57 over 5 mins. The spontaneous spike rate was generally low, as reported for young neurons generated in adult hippocampus that tend to produce fewer bursts than mature neurons. SCN OPCs also differentiated into mature oligodendrocytes according to increased myelin basic protein expression. We conclude that mature SCN tissue has the ability to form additional neurons that could enable plasticity within SCN neural circuits and modify circadian rhythms adaptively.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.06/A6

Topic: A.02. Postnatal Neurogenesis

Support: NSF Grant 1538505

Title: Stochastic cellular automata model of neurosphere growth: Roles of proliferative potential, contact inhibition, cell death, and phagocytosis

Authors: *G. K. ZUPANC, R. SIPAHI

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Abstract: Neural stem and progenitor cells isolated from the central nervous system form, under specific culture conditions, clonal cell clusters known as neurospheres. The neurosphere assay has proven to be a powerful *in vitro* system to study the behavior of such cells and the development of their progeny. However, the theory of neurosphere growth has remained poorly understood. To overcome this limitation, we have, in the present paper, developed a cellular automata model, with which we examined the effects of proliferative potential, contact inhibition, cell death, and clearance of dead cells on growth rate, final size, and composition of neurospheres. Simulations based on this model indicated that the proliferative potential of the founder cell and its progenitors has a major influence on neurosphere size. On the other hand, contact inhibition of proliferation limits the final size, and reduces the growth rate, of neurospheres. The effect of this inhibition is particularly dramatic when a stem cell becomes encapsulated by differentiated or other non-proliferating cells, thereby suppressing any further mitotic division — despite the existing proliferative potential of the stem cell. Conversely, clearance of dead cells through phagocytosis is predicted to accelerate growth by reducing contact inhibition. A surprising prediction derived from our model is that cell death, while resulting in a decrease in growth rate and final size of neurospheres, increases the degree of differentiation of neurosphere cells. It is likely that the cellular automata model developed as part of the present investigation is applicable to the study of tissue growth in a wide range of systems.

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Topic: A.02. Postnatal Neurogenesis

Support: NIH NIMH R01, MH083804

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NYSTEM Einstein Training Program in Stem Cell Research C30292GG

Title: FGFRs regulate proliferation and dendritogenesis in adult-born dentate gyrus neurons

Authors: *M. GRONSKA-PESKI, J. M. HEBERT

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Abstract: Neurogenesis, or generation of new neurons, is very limited in the adult mammalian brain. The hippocampal dentate gyrus (DG) is one of two well established neurogenic niches in

mice and its study has potential therapeutic value for age-related memory decline and cell replacement. Fibroblast Growth Factor Receptors (FGFRs)1-3 and their various ligands are differentially expressed throughout the rodent brain where they play major functions in stem cell development and survival. Yet, molecular pathways that utilize FGFRs to guide the generation, maturation and integration of newly born neurons are poorly understood. We previously showed that loss of FGFR1-3 in DG adult-born stem cells and early progenitors leads to decreased stem cell maintenance and progenitor cell proliferation. However, roles for FGFR-dependent intracellular signaling on other steps of neurogenesis are currently unknown. To address this knowledge gap, we are examining stem/progenitor cell proliferation and dendritic elaboration in the DG of FGFR1-3 conditional mutant mice. We found that loss of FGFR1-3 in neurogenic cells generates defects in cell maintenance and dendritic growth. Stem/progenitor cells also display a defect in proliferation after placement in the enriched environment, suggesting a significant role of FGFR in this process, which until now had been mainly attributed to BDNF-TrkB signaling. Using FGFR1 mutants that lack binding sites for the downstream mediators Phospholipase-C gamma (PLC γ) or Fgf Receptor Substrate (FRS) proteins, we demonstrated that both FRS and PLC- γ are non-redundantly required to maintain stem/progenitor cell numbers in the DG, possibly by promoting stem cell expansion. Unexpectedly, FGFR1-PLC- γ mutants had a dendritic overgrowth phenotype in immature neurons while FGFR1-FRS mutants displayed no dendritic phenotype, suggesting a novel role for FGFR1-PLC γ signaling. We are currently conducting experiments to understand FGFRs' mechanisms of action on dendritogenesis and cell proliferation. Determining which intra- and extracellular pathways differentially affect adult stem cell expansion and the maturation of new neurons will provide better potential therapeutic targets for reversing deficiencies that lead to age-related memory decline. Understanding the diversity of FGFRs' modes of action in the adult brain neurogenic niche may have implications for understanding their functions besides their canonical roles in embryonic brain development.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

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Title: Morphological changes and migration termination of newborn neurons controlled by PlexinD1 signaling

Authors: *M. SAWADA¹, N. OHNO^{2,3}, M. KAWAGUCHI⁴, S.-H. HUNAG¹, T. HIKITA¹, Y. SAKURAI¹, H. NGUYEN², T. THAI², Y. ISHIDO¹, Y. YOSHIDA⁵, H. NAKAGAWA⁴, A. UEMURA¹, K. SAWAMOTO^{1,2}

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Abstract: Precise regulation of the maintenance and termination of neuronal migration is required for the development and function of the postnatal brain. Newborn neurons maintain a very simple, bipolar shape while they migrate from their birthplace toward their destinations in the brain, where they differentiate into mature neurons with complex dendritic morphologies. Intrinsic and extrinsic mechanisms regulate the migration termination of newborn neurons. Moreover, during migration termination, prominent changes in cell morphology, involving the extension of cellular protrusions, are observed and lead to the development of highly organized dendrites and functional circuits. However, how the morphological changes that occur during neuronal migration termination are regulated remains unknown. Here we report a mechanism by which the migration termination of newborn neurons is maintained in the postnatal olfactory bulb (OB). During neuronal deceleration in the OB, newborn neurons transiently extend a protrusion from the proximal part of their leading process in the resting phase, which we refer to as a filopodium-like lateral protrusion (FLP). The FLP formation is induced by PlexinD1 downregulation and local Rac1 activation, which coincide with local microtubule reorganization and the pausing of somal translocation. Photoactivation techniques revealed that the somal translocation of resting newborn neurons is suppressed by microtubule polymerization within the FLP. The timing of migration termination of newborn neurons, controlled by Sema3E-PlexinD1-Rac1 signaling, influences the neurons' final positioning, dendritic patterns, and functions in the postnatal OB. These results suggest that PlexinD1 signaling controls FLP formation and the migration termination of newborn neurons through a precise control of microtubule dynamics. This mechanism also highlights the importance of morphological regulation of migrating neurons for the proper positioning of cells in neuronal circuits.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

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Topic: A.02. Postnatal Neurogenesis

Support: NCN Grant Harmonia 2014/14/M/NZ4/00561

Title: Nuclear shape of adult neural stem cells in mouse dentate gyrus

Authors: ***R. FILIPKOWSKI**¹, A. W. GRYMANOWSKA¹, A. MARTIN², K. H. OLSZYNSKI¹, G. M. WILCZYNSKI², A. SZCZEPANKIEWICZ², K. NOWINSKI³, B. BORUCKI³, A. MAGALSKA²

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Abstract: The cellular and molecular properties of adult neural stem cells (aNSCs) in the dentate gyrus (DG) remain largely unknown. The nuclear shape patterns of aNSCs have never been described before in a systematic way. Here we have confirmed the heterogeneity of aNSCs cells in terms of their nuclear morphology. Namely, we have analyzed nuclear shape of type 1 (Nestin-GFP+, radial process), type 2a (GFP+/DCX-, no radial process), type 2b (GFP+/DCX+), and type 3 (GFP-/DCX+) cells as well as neurons (NeuN+) using Nestin-GFP transgenic mice. The images were collected with confocal and electron microscopy. We have determined the nuclear shape differences by calculating roundness, circularity and solidity of two-dimensional middle sections of DAPI-stained nuclei. We have also performed morphometric analysis of the nuclei using a newly designed add-on for a computer program, VisNow, to limit DAPI-positive region of interest and calculate their three-dimensional properties. These allowed us to describe the nuclear morphology in a lineage progression. We have found putative envelope-like chromatin sheets in type 1 cells. Similar structures were recently reported in quiescent aNSCs of the subventricular zone. Nuclear shape changes are connected with the function of the cell. The nuclei of most cells are either round or oval, while altered nuclear shapes are observed in some diseases, e.g. Hutchison-Gilford progeria syndrome or cancer. Moreover, in certain specialized cell types, altered nuclear shape is important for the function e.g. multi-lobed nuclei in neutrophils gives them ability to migrate through small openings. Finally, several studies have indicated that the specific gene location in the nucleus influences its activity. This location is a result of chromatin reorganization which is hypothesized to depend, among others, on nuclear shape changes. Our results are an initial description of the nuclear shapes of neurogenic cell line. What determines nuclear shape of aNSCs and how does the shape affect cell functioning remains

unclear. We hope our results will bring new insights into understanding the cellular properties of aNSCs.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

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Topic: A.02. Postnatal Neurogenesis

Support: Marmara University Scientific Research Committee SAG-K-081117-0608

Title: Developmental evaluation of doublecortin immunoreactivity at light microscopic level in Wistar albino rats

Authors: ***O. T. KAYA**, S. D. YILDIZ, C. KANDEMIR, U. S. SEHIRLI, S. SIRVANCI
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Abstract: Introduction: Neurogenesis is the formation of functional neurons from progenitor cells which starts at the embryonic period and continues during lifetime in hippocampal dentate gyrus and subventricular zone of the lateral ventricle in adult brain.

Methods: In this study, we aimed to investigate developmental process of neurogenesis in the hippocampus of Wistar albino rats. For this purpose, brains were obtained from 7-, 14-, and 21-day-old male Wistar rats by intracardiac perfusion fixation with 4% paraformaldehyde and processed for immunohistochemical and immunofluorescence assessments. 5 µm-thick paraffin sections were labelled with anti-doublecortin (anti-DCX) antibody, as a marker of newly born neuroblasts, to determine neurogenesis. For light microscopic imaging, 3,3'-diaminobenzidine was used as a chromogen, whereas DyLight-550 conjugated secondary antibody was used for fluorescence microscopical imaging. Stained sections were examined by a brightfield and fluorescence microscope attached to a CCD camera.

Results: DCX immunoreactive cells were dispersed throughout the granular and subgranular layers of the hippocampal dentate gyrus in 7-day-old group.

However, in 14- and 21-day-old groups, DCX immunoreactive cells were observed only in the subgranular zone in the sections labelled both with the two different types of staining methods.

Conclusion: According to the data from this study, DCX immunoreactive cells may be localized in different parts of the dentate gyrus during developmental process. Further studies are needed in order to understand the mechanism by which the cells at the different levels of the granular

layer in 7-day-old rats end up to be localized at the subgranular layer in later stages of development.

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Poster

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Title: Postnatalsubventricular zone neurogenesis:Regulation by adenosine A_{2A} receptors

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Abstract: Constitutive neurogenesis takes place in both adult mammalian subventricular zone of the lateral ventricle and in the subgranular zone of the dentate gyrus (DG) in the hippocampus. This study evaluated whether adenosine A_{2A} receptors (A_{2A}Rs) have a role in postnatal SVZ neurogenesis and if they are required for brain-derived neurotrophic factor (BDNF)-induced neurogenesis, namely in cell proliferation and neuronal differentiation, and for the capacity of progenitor cells to divide and self-renew within the SVZ. Results using SVZ-derived neurosphere cultures demonstrated that neither A_{2A}R agonist (CGS21680, 30 nM), A_{2A}R antagonist (ZM241385, 50 nM) nor BDNF (30ng/ml), altered cell viability (measured by propidium iodide staining). A cell-fate study was also performed using an immunocytochemistry against Sox2 (a marker of neural stem cells with the ability to self-renew). Neither A_{2A}R activation nor blockade changed the number of Sox2^{+/+} SVZ cell-pairs derived from a progenitor cell division. Furthermore, neither proliferation (measured by BrdU staining) nor neuronal differentiation (measured by NeuN staining) of cultured cells were affected by either A_{2A}R agonist or antagonist incubation alone. Importantly, the *in vitro* data was corroborated in an *in vivo* 6-week-old rat model, where CGS 21680 (100 nM) was intraventricularly delivered

for 28 days and BrdU was administered in the first 3 days of the treatment. In fact, A_{2A}R activation did not change proliferation nor neuronal differentiation (measured by BrdU and NeuN double-staining) *in vivo*. Nevertheless, BDNF enhancement of cell proliferation and neuronal differentiation *in vitro* was completely prevented by A_{2A}R antagonist. Conversely, A_{2A}R agonist enhanced axonal and dendritic length and branching of SVZ-derived neurons. Taken together, data here described reveal a novel role for A_{2A}Rs as modulators of SVZ neurogenesis, with A_{2A}R endogenous activation being crucial for BDNF-mediated actions, as well as in axonal and dendritic growth.

Disclosures: F.F. Ribeiro: None. F. Ferreira: None. R.S. Rodrigues: None. R. Soares: None. S.H. Vaz: None. S. Solá: None. H. Mira: None. A.M. Sebastião: None.

Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.12/A12

Topic: A.02. Postnatal Neurogenesis

Support: LISBOA-01-0145-FEDER-007391, project co-funded by FEDER through POR Lisboa 2020 (Programa Operacional Regional de Lisboa) from PORTUGAL 2020 FCT Grants PTDC/DTP-FTO/3346/2014, SFRH/BD/129710/2017 and iFCT, IF/01227/2015
SynaNet H2020 Twinning Action (GA-692340)

Title: Crosstalk between cannabinoid and adenosine A_{2A} receptors modulating postnatal neurogenesis

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Abstract: Postnatal neurogenesis occurs in dedicated niches of the mammalian brain in a process modulated by cannabinoid type 1 and 2 receptors (CB1R and CB2R). Recent evidence sheds light on the interaction of adenosine A_{2A} receptors (A_{2A}R) with cannabinoid receptors in striatal synaptic transmission. Herein we aimed at understanding the putative role of A_{2A}R on cannabinoid-mediated cell fate, cell proliferation and neuronal differentiation of rat neonatal subventricular zone (SVZ) and dentate gyrus (DG) postnatal neurogenesis. SVZ and DG neurospheres, obtained from early postnatal (P1-3) Sprague-Dawley rats, were prepared in serum-free medium (SFM) containing growth factors. Resulting neurospheres were exposed to

pharmacological relevant concentrations of A2AR agonist CGS21680 (30nM), A2AR antagonist ZM241385 (50nM), CB1R agonist ACEA (1 μ M), CB1R antagonist AM251 (1 μ M), CB2R agonist HU-308 (1 μ M) or CB2R antagonist AM630 (1 μ M). For the cell-fate studies, dissociated cells were treated for 24h with the drugs, and were stained for Sox2 (marker of neural stem/progenitor cells - NSPCs). Cell pairs resulting from the division of a single NSPC were counted and categorized in 3 groups according to their Sox2 expression: in both daughter cells (Sox2+/+), in only one of the daughter cell (Sox2+/-) and no expression (Sox2-/-). Cell proliferation was analyzed by BrdU (10 μ M) staining and neuronal differentiation by neuronal nuclear (NeuN) immunocytochemistry. CB2Rs or A2AR activation was found to promote self-renewing divisions of DG cells (n=6, p<0.01). Importantly, A2AR antagonist blocked the effect mediated by CB2R activation, while CB1R or CB2R antagonists blocked A2AR-mediated effect. SVZ cell proliferation was only affected by CB1R activation (n=7, p<0.001), an effect blocked in the presence of an A2AR antagonist. Although CB1R, CB2R or A2AR activation alone did not alter DG cell proliferation, CB1R or CB2R co-activation with A2ARs promoted a significant increase in DG cell proliferation (n=5, p<0.001). Lastly, CB1R and/or CB2R activation promoted SVZ (n=5, p<0.001) and DG (n=5, p<0.001) neuronal differentiation, while A2AR activation only promoted DG neuronal differentiation (n=5, p<0.001). In both cases, the proneurogenic effect mediated by CB1R or CB2R agonists was blocked by an A2AR antagonist (n=5, p<0.001), while in DG the A2AR-mediated actions on neuronal differentiation were blocked by CB1R or CB2R antagonists (n=5, p<0.001). Taken together, our findings suggest an interaction between the cannabinoid and adenosinergic systems, cross-antagonism being evident, responsible for controlling early stages of postnatal neurogenesis.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.13/A13

Topic: A.02. Postnatal Neurogenesis

Support: Fundação para a Ciência e a Tecnologia (FCT) PhD fellowship - SFRH/BD/74662/2010

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Fundação para a Ciência e a Tecnologia (FCT) PTDC/DTP-FTO/3346/2014 and iFCT, IF/01227/2015

Title: Postnatal hippocampal neurogenesis: Regulation by adenosine A2A receptors

Authors: *F. F. RIBEIRO^{1,2}, F. FERREIRA^{1,2}, R. S. RODRIGUES^{1,2}, R. SOARES^{1,2}, S. SOLÁ³, H. MIRA⁴, A. M. SEBASTIÃO^{1,2}, S. XAPELLI^{1,2}

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Abstract: Constitutive neurogenesis takes place in both adult mammalian subventricular zone of the lateral ventricle and in the subgranular zone of the dentate gyrus (DG) in the hippocampus. This study evaluated whether adenosine A_{2A} receptors (A_{2A}Rs) have a role in postnatal DG neurogenesis, namely in cell proliferation and neuronal differentiation, and for the capacity of progenitor cells to divide and self-renew within the DG.

Results using rat DG-derived neurosphere cultures demonstrated that A_{2A}R agonist (CGS21680, 30 nM) enhanced viability of neuronal cells (measured by propidium iodide and doublecortin (DCX) double-staining) and proliferation of neuronal progenitor cells (measured by BrdU and DCX double-staining). Moreover, a cell-fate study was performed using an immunocytochemistry against Sox2 (a marker of neural stem cells with the ability to self-renew). A_{2A}R agonist treatment promoted an increase in the number of Sox2^{+/+} cell-pairs derived from a progenitor cell division, which is in accordance with an increase of the self-renewal capacity of progenitor cells mediated by A_{2A}R activation. Furthermore, A_{2A}R activation promoted an increase in the percentage of new mature neurons (measured by NeuN staining). Importantly, the *in vitro* data was corroborated in an *in vivo* 6-week-old rat model, where CGS 21680 (100 nM) was intraventricularly delivered for 28 days and BrdU was administered in the first 3 days of the treatment. In fact, it was shown that A_{2A}R activation promoted an increase in the number of BrdU⁺/NeuN⁺ double-positive cells, while promoting an increase in dendritic arborisation. Taken together, A_{2A}R activation enhances postnatal hippocampal neurogenesis both *in vitro* and *in vivo*.

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Poster

029. Postnatal Neurogenesis: Temporal and Spatial Patterns

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 029.14/A14

Topic: A.02. Postnatal Neurogenesis

Title: The effects of electromagnetic fields on planarian neuroregeneration

Authors: *L. THOMPSON¹, E. BORSUK¹, K. DENESOPOLIS¹, S. R. GUARIGLIA²
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Abstract: An electromagnetic field, or EMF, is a property of space which is created by an electric charge moving around. An electric charge by itself produces only an electric field; however, when the charge is in motion, a magnetic field is generated as well. When the electromagnetic fields are exposed to one another, they combine to form an electromagnetic field. We are exposed to EMFs every day, as all appliances and computers emit EMFs. Recent studies have shown that EMF exposure has a significant impact on varying aspects of human health, and may be associated with stress, tumor formation, and immune system depression. Planarians are free-living flatworms that have the unique ability to regenerate. Tissue regeneration, germ-cell specification, tissue remodeling, and adult tissue maintenance in planarian, include a large group of undifferentiated cells known as neoblasts, or planarian stem cells, which are located throughout the body and that continuously divide. During regeneration, these cells are the source of new tissue. Both humans and planarians share several genes that are expressed in stem cells. In our research, we aim to see the effects that EMFs have on planarian neuroregeneration. To accomplish this task, we have amputated the heads from planaria and allowed them to regenerate in a 0.75 uTesla (uT) EMF for seven days, which is the time that is needed for head and brain regeneration. We examined their locomotor activity using a planarian locomotor velocity assay (pLMV) and an automated locomotor assay. We also examined their ability to learn using a passive avoidance assay and examined the number of neurons that were regenerated over seven days. We have found that there is a significant increase in locomotor activity found in our EMF groups, which begins as early as Day 3 postamputation, suggesting accelerated neural regeneration. We have also found that at Day 7 post-amputation, the EMF group has a significantly greater number of neurons in the newly developed brain. With respect to behavior at seven days post amputation, we have found that EMF planarians no longer show locomotor differences once regeneration is complete, but do show enhanced motion in the periphery of an open field, suggesting that they do have a more anxious phenotype. Finally, we found that planarians exposed to EMFs for the entire course of early neurodevelopment show reduced capacity to actively avoid a shock stimulus, suggesting impaired learning ability. The sum of our data shows that there may be some enhancement in neuroregeneration in response to EMF exposure, which has application in neuroregeneration, but a prolonged duration of exposure may result in unwanted, deleterious effects.

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Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.01/A15

Topic: A.07. Developmental Disorders

Support: MHV Grant PMPDP3_171309

Title: The role of gene-by-environment interactions in autism spectrum disorders

Authors: *F. HOLLIS, C. MUNOZ CASTILLO, V. MARIANO, A. KANELLOPOULOS, C. BAGNI

Dept. of Fundamental Neurosciences, Univ. De Lausanne, Lausanne, Switzerland

Abstract: Autism spectrum disorders (ASD) have a serious impact on public health, with greater than 1% of the world's population afflicted with an ASD. In addition to cognitive impairment, symptoms can also include impaired social interactions, repetitive behaviors, disrupted sleep, and hyperactivity. While studies have identified a clear genetic component, with a number of overlapping genes that show strong associations with ASD, at least 40% of ASD cases remain unexplained by genetics alone. Given the increasing numbers of ASD diagnoses, environmental exposures may interact with genetic backgrounds to induce ASD symptoms. Here we investigated the interactions between toxin exposure during key developmental time points and specific ASD-risk genes using the model *Drosophila melanogaster*. We exposed different *Drosophila* mutants to insults, or control conditions, and assessed them for ASD-like phenotypes. We found that exposure to environmental insults during development had important effects on developmental trajectories and metabolism that differed between mutants for ASD candidate genes, highlighting a role for the interaction between the environment and genotype in ASD.

Disclosures: F. Hollis: None. C. Munoz Castillo: None. V. Mariano: None. A. Kanellopoulos: None. C. Bagni: None.

Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.02/A16

Topic: A.07. Developmental Disorders

Support: NIEHS 5R01ES025549-02
NSF GRFP

Title: Prenatal air pollution and maternal stress alter brain development in the anterior cingulate cortex

Authors: *C. L. BLOCK¹, S. D. BILBO², C. EROGLU³

¹Psychology and Neurosci., Duke Univ., Durham, NC; ²Pediatrics, Harvard Med. School/MGH, Charlestown, MA; ³Cell Biol Dept, Duke Univ, DUMC, Durham, NC

Abstract: Prenatal air pollution (diesel exhaust particles; DEP) combined with maternal stress (MS) during the last trimester of gestation act synergistically on offspring to promote long lasting changes in neuroimmune function and deficits in behavior in adulthood. Microglia are the primary immune cells in the CNS, they are important in immune host defense and are involved normal brain development. Previous research has demonstrated that microglia are abnormal in several neurodevelopmental disorders, and in rodent models, transgenic manipulation of microglia number or function results in brain dysfunction. However, it is unclear whether environmentally relevant immune activation produces a similar phenotype. In this study, we aimed to determine whether prenatal DEP and MS (DEP+MS) alter social behaviors, microglia infiltration and cortical development in the anterior cingulate cortex in offspring. Pregnant mouse dams were intermittently exposed via oropharyngeal aspiration to DEP (50 $\mu\text{g} \times 6$ doses) or vehicle (VEH) throughout gestation. This exposure was combined with standard housing for dams or nest material restriction (a model of maternal stress) during the last third of gestation. Prenatal DEP+MS altered social communication behavior in developing offspring. At postnatal day 15, prenatal DEP+MS resulted in changes in synaptic connectivity, development of microglia and astrocyte distribution in cortical regions implicated in autism. Taken together, these results suggest that environmental risk factors can alter microglia development/function, resulting in changes in brain development commonly seen in autism. This model thus affords a unique opportunity to explore environmentally relevant cellular and molecular mechanisms that contribute to neurodevelopmental disorders.

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Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.03/A17

Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks Family Foundation

Title: 17- β -estradiol may be a potential influence factor in a mouse model of maternal antibody induced autism spectrum disorder

Authors: *A. GATA GARCIA^{1,3}, L. BRIMBERG¹, B. DIAMOND¹, B. T. VOLPE²

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Abstract: Autism spectrum disorders (ASD) are defined as a group of neurodevelopmental conditions characterized by impaired social interactions and communication, repetitive behaviors, and restricted interests or activities. The prevalence of ASD has been increasing over the past decades, reaching 1 in 59 in 2014. Among those affected, males are disproportionately represented (4 males per 1 female affected). Two main factors, sex chromosomes and gonadal hormones, have been proposed to drive this sex bias in ASD. It is hypothesized that both sex chromosomes and gonadal hormones play a role in ASD susceptibility during prenatal and early postnatal periods when alterations in brain development may have irreversible anatomical and behavioral effects.

As in humans, our mouse model of maternal brain-reactive antibody induced ASD shows a sex bias. Only the male mice exposed *in utero* to C6, a maternal brain-reactive monoclonal antibody to Contactin Associated Protein-Like 2 (Caspr2) isolated from the serum of a mother of a child with ASD, have neuroanatomical abnormalities and ASD-like behaviors. Specifically, C6 exposed male C57BL/6 mouse fetuses (E15.5) have a thinner cortical plate and fewer progenitor cells in the ventricular zone. Furthermore, these mice have impaired social interactions, inflexible learning, and increased repetitive behaviors as adults.

We have evaluated the influence of sex chromosomes and gonadal hormones on the susceptibility to C6 in mice. For this purpose, we used the “Four Core Genotype” (FCG) mouse model which uncouples gonadal sex development from sex chromosome complement therefore allowing for the isolation of genetic from hormonal determinants of sex-specific phenotypes. We found that presence of the Y chromosome alone explained the sex bias observed in cortical plate thickness in the fetus; thus, XY⁻ Sry and XY⁻ mice both exhibited a thinned cortical plate. In contrast, impaired social interactions in response to C6 were seen only in mice with Y chromosome and male gonadal development.

Given the role of gonadal hormones that we have identified, we hypothesize that estrogen treatment can reverse C6 induced ASD-like behavioral phenotypes. Early postnatal treatment with estrogen has been shown to reverse ASD-like phenotypes in Caspr2 knockout zebrafish and reeler heterozygous mice. We are following a similar paradigm in which we administer 17- β -estradiol or placebo to dams to enrich estrogen exposure in breastfeeding pups exposed *in utero* to C6 or B1 isotype control. This study will further elucidate the role of estrogen in ASD while also offering the opportunity to identify potential therapeutic targets downstream of gonadal hormones.

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Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

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Program #/Poster #: 030.04/A18

Topic: A.07. Developmental Disorders

Support: UC MEXUS

APS Integrative Organismal Systems Physiology (IOSP) Fellowship

UC Chancellor's Fellowship

Graduate Division Fellowship

Title: Neuroanatomical correlates in mice perinatally exposed to indoor flame retardants showing abnormal affective and social behavior

Authors: *E. KOZLOVA^{1,2}, J. M. KRUM¹, L. ANCHONDO¹, N. HUFFMAN¹, S. UDDIN¹, M. NABATANZI³, V. CARRILLO¹, B. D. CHINTHIRLA¹, M. C. CURRAS-COLLAZO¹
¹Molecular, Cell and Systems Biol., ²Interdepartmental Neurosci. Grad. Program, ³Dept. of Psychology, Univ. of California Riverside, Riverside, CA

Abstract: Polybrominated diphenyl ethers (PBDE) are indoor flame retardant pollutants with adverse neurobehavioral effects. In humans, PBDEs are associated with lower psychomotor and mental development, reduced IQ scores, poorer attention, and increased psychological stress and anger. Results from studies on experimental animals that are developmentally exposed to PBDEs support an association between PBDEs and neurobehavioral deficits. This study examined whether perinatal exposure to an industrial penta-BDE mixture alters affective and sensorimotor behaviors and neuroanatomical correlates in affected mice offspring. C57BL/6 dams were orally dosed with DE-71: corn oil vehicle control (OD), low dose (LD) (0.1 mg/kg/d), or high dose (HD) (0.4 mg/kg/d). Adult male offspring were subjected to behavioral testing at postnatal day (PND) 40-80 for social memory (social recognition task (SRT)), sensorimotor integration/anxiety (Suok) and depressive-like behavior (forced swim (FS)). Male HD offspring exhibited deficits in SRT ability relative to OD ($p < .0001$), showing no preference to investigate a novel versus familiar mouse. This was not due to deficits in ability to discriminate between attractive or aversive scents as measured by an olfactory preference test (OPT). On Suok, HD males showed significantly less falls/segments crossed ($p = .024$), indicating altered sensorimotor ability. In EPM, LD males showed significantly more time in open arm ($p = .017$). FS did not indicate changes in time spent immobile across groups. Female offspring showed similar effects except on EPM. To investigate cortical neurodevelopment after perinatal DE-71 exposure, intraneocortical and thalamocortical connections (INCs) in PND 7 male offspring were examined using post mortem anatomical dye tracing. DiI and DiA lipophilic tracer dyes were injected into the frontal and visual cortices of hemisected brains, respectively. Fluorescent staining was

localized to cortical layers containing retrogradely labelled cells. The anatomical specificity of injection and complete dye transport was verified by corresponding thalamocortical labelling. Additionally, gross anatomical measures were performed on sections stained for Nissl substance to examine if abnormal cortical and subcortical anatomy correlates with atypical behavior. Our findings provide novel information on neuroanatomical correlates of disrupted adult social, anxiety and sensorimotor behavior after developmental exposure to environmentally relevant PBDEs.

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Poster

030. Environmental and Immunological Influences on Autism

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Program #/Poster #: 030.05/A19

Topic: A.07. Developmental Disorders

Support: NIH Grant P01 PAR-10-245
MGH ECOR Deliberative Support Funding

Title: Modeling Pitocin administration at birth: How does exogenous oxytocin affect the developing brain and gastrointestinal system?

Authors: *M. A. KINGSBURY¹, A. M. PERKEYBILE², J. R. YEE³, W. M. KENKEL², J. Y. LEBRON-ECHANDY³, S. D. BILBO¹, C. S. CARTER^{4,2}

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Abstract: The current study investigates whether the modulation of oxytocin (OT) signaling at birth alters the developing brains and guts of offspring. Approximately 23-50% of pregnant women in the US receive synthetic oxytocin (sOT; Pitocin) to induce or augment labor (Declercq et al., 2014; Hamilton et al., 2015), yet little is known about the long-term neurological or gastrointestinal consequences of such interventions or whether there are dose-dependent effects. Recent studies suggest that sOT administration at birth is associated with an increased risk for autism (Gregory et al., 2013; Smallwood et al., 2016; Friedlander et al., 2017) while other research has found no association or small effect sizes (Guastella et al., 2018). Patients with autism are often characterized with gastrointestinal disturbances, dysfunction and/or disease (Kelly et al., 2017). Importantly, maternal oxytocin at birth protects the fetal brain during delivery from hypoxia and limits inflammation mediated by microglial cells (Tyzio et al., 2006; Khazipov et al., 2008; Yuan et al., 2016). Separate research shows that oxytocin is anti-

inflammatory within the gut (Welch et al., 2014) and promotes normal enterocyte development (Klein et al., 2013; 2016). Here we examine how different doses of sOT at birth impact 1) oxidative stress exposure, microglial activation, parvalbumin interneuron (PVI) number and perineuronal net (PNN) formation in the brain and 2) gastrointestinal structure and gene expression patterns in the gut of postnatal and adult offspring. We hypothesize 1) that endogenous OT released during labor promotes the proper formation of neural circuitry and gastrointestinal structure by limiting inflammation within both systems and 2) that changes in OT concentration modify neural circuitry and gut architecture, particularly at high doses. To test these hypotheses, we examined the brains of male and female offspring born to female prairie voles that either experienced a vaginal birth with no drug manipulation or received an injection of sOT just prior to a vaginal birth. We used 3 doses of sOT to examine the dose response of sOT on brain and gut development. We found that sOT administration to pregnant dams altered microglial density, the number of PNNs and the number of PVIs surrounded by PNNs in treated offspring compared to control offspring. We also observed changes in the structure of the gut epithelium of offspring exposed to sOT at birth, as well as sOT dose-dependent changes in the gene expression of pro-inflammatory cytokines and tight junction proteins in the gut. We anticipate our results will aid in the evaluation of treatments used to manage childbirth.

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Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

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Program #/Poster #: 030.06/A20

Topic: A.07. Developmental Disorders

Support: NIH Grant R01ES025549
Paul and Janis Cunningham

Title: Sex-biased mitochondrial and behavioral alterations following early-life immune activation

Authors: *E. A. BORDT¹, K. H. JIANG¹, C. J. SMITH¹, S. D. BILBO²

¹Lurie Ctr. for Autism, Massachusetts Gen. Hosp., Charlestown, MA; ²Pediatrics, Harvard Med. School/MGH, Charlestown, MA

Abstract: Autism Spectrum Disorders (ASDs) are a collection of complex neurodevelopmental disorders characterized by repetitive behavior and alterations in social interaction/communication. ASD occurs in ~1 in 68 children in the US, with a strong sex bias in prevalence (~4 males affected to every female). Postmortem analyses of brains from children

with ASD revealed significant decreases in expression of mitochondrial electron transport chain (ETC) subunits, while other analyses have found evidence for immune activation in these brains. However, reports often fail to distinguish between cell type or sex of the patients. Increasing evidence suggests that mitochondrial respiratory function is inhibited during proinflammatory activation of microglia, the innate immune cells of the brain. Using *both* whole transcriptome profiling with Next Generation RNA sequencing and PCR Array of isolated microglia (CD11b bead isolation) from mice injected perinatally with the bacterial endotoxin lipopolysaccharide (LPS), we found that ~96% of ETC genes were strongly (>20%) diminished by LPS in male microglia. Only ~6% of ETC genes were comparably decreased in females, suggesting that reduced mitochondrial function may be implicated in microglial activation, *particularly in males*. We are currently examining whether this perinatal immune challenge results in sex differences in microglial mitochondrial morphology, a metric thought to be impacted by immune challenge that is intricately linked to mitochondrial function. We show that perinatal LPS resulted in decreased social exploration in both sexes at PN15, but with larger effects in males. By PN60, perinatal LPS treatment resulted in decreased sociability and social novelty seeking in males only. These data indicate sex-biased deficits in social interaction and anxiety that are related to clinical manifestations of ASD. We are currently testing the hypothesis that the perinatal hormone (testosterone) surge in males around the time of birth may impart male susceptibility to immune challenge.

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Poster

030. Environmental and Immunological Influences on Autism

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Program #/Poster #: 030.07/A21

Topic: A.07. Developmental Disorders

Support: KAKENHI Grant 16H02657
KAKENHI Grant 16K09694
KAKENHI Grant 17K19663

Title: Mice exposed to postnatal allergy show abnormal behavior and dysregulated gene profile related to autism spectrum disorder only in male

Authors: *B.-Y. SAITOH, R. YAMASAKI, D. V. KRUINING, C. THOMSEN, J.-I. KIRA
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Abstract: Background: Rapid increase in the prevalence of neurodevelopmental disorders and allergic diseases has recently been observed in advanced countries. In autism spectrum disorder (ASD), both genetic heritability and environmental factors (i.e., maternal infection) are important

risk factors. ASD is more prevalent in male than female; however, the reason for such gender difference remains unknown and no ASD model reproduce such gender-related difference. Several epidemiological surveys show that mothers with allergy exhibit increased risk of having children with ASD. Thus, we hypothesize that allergy may enhance susceptibility to neurodevelopmental disorders. We investigated whether neonatal allergen exposure affects behavior and brain pathology in mice.

Methods: Female mice (4-week-old C57BL/6J) received 1 mg of alum by intraperitoneal injection on days 1 and 14. On day 15, potential mothers were mated with adult male mice. After birth, pups were subjected to inhalation of PBS or ovalbumin (OVA) for 30 min/day, 3 times/week. At P14, immunohistochemistry, western blotting, and microarrays were performed on hippocampal tissue. After weaning, pups were behaviorally tested at 3 week intervals by three-chamber test (TCT), self-grooming test (SGT), and marble-burying test (MBT).

Results: In the TCT, only males from OVA group spent significantly shorter in the unfamiliar chamber compared with males from control group. Similarly, in the SGT and MBT, OVA group males spent significantly longer self-grooming and buried significantly more marbles than control group mice. Western blotting showed significant downregulation of synaptic proteins in OVA group males compared with control group males. Immunohistochemistry revealed regional microglial activation in the male OVA group compared with the male control group. Microarray enrichment analysis showed significantly enriched Gene Ontology terms, such as axon guidance, and synaptic transmission, in OVA group males than control group males. Comparative gene expression analysis identified shared, albeit partially, dysregulated genes between our maternal allergy model and published gene datasets of genetic ASD and polyinosinic:polycytidylic acid (Poly I:C) ASD models.

Conclusions: Our results suggest that allergy in the postnatal period can impair normal synaptogenesis and induce an ASD-like phenotype only in male, which supports a link between maternal allergy and male offspring with ASD.

Disclosures: **B. Saitoh:** None. **R. Yamasaki:** None. **D.V. Kruining:** None. **C. Thomsen:** None. **J. Kira:** None.

Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.08/A22

Topic: A.07. Developmental Disorders

Support: Scholarship Conacyt No. 575611 (JAPR)

Title: Modification in the expression of GABA receptors in the cerebellum of autistic rats subjected to an enriched environment at different ages

Authors: ***J. A. PEREZ**¹, **O. CRUZ**², **L. GARCÍA**³, **G. CORIA AVILA**³, **M. TOLEDO**³, **M. HERNÁNDEZ**³, **J. MANZO**³

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Abstract: Autism is a neurodevelopmental disorder that causes a spectrum of heterogeneous behaviors, having as common denominator problems in social interaction and alterations in both communication and movement. Also, another common denominator is the alteration of the cerebellum, which presents a reduction in size and a significant decrease in the GABAergic neurotransmission. Considering the central role of GABA in the functioning of the cerebellum, in this project we were interested in analyzing the density of its receptors in an autistic rat model, and the impact of the stimulation of the subjects by an enriched environment. Thus, we did an immunohistochemical analysis of GABA receptors (rGABA) as a basis for the study of this neurotransmitter in the spectrum. We used an autistic Wistar rat model obtained after postnatal injection of a daily dose of 150 mg/kg of valproic acid to pups from day P6 to P12. Four groups of males were used, Controls (Ct) in standard (SE) and enriched (EE) environment, and Autistic (At) in SE and EE. Then, rGABA in the vermis of the cerebellum was quantified. The results showed that At subjects presented a significant reduction of rGABA, whose density increased to level Ct after being exposed to an enriched environment. The results show that no matter the reduction of rGABA in autistic subjects, the enriched environment has an optimal impact in its density. Therefore, data shows non-pharmacological benefits that can be applied to subjects within the spectrum, possibly prompting appropriate modifications in their behavioral displays, which will be analyzed in future studies. In our laboratory we have observed that the postnatal model replicates effects on GABAergic neurotransmission only in male rats, and stimulation with the enriched environment has a positive effect on the expression of these rGABA. Therefore we delayed the application of the enriched environment to observe the effect of it in older subjects (P90), having the same four groups analyzed in the age of P30.

Scholarship Conacyt No. 575611 (JAPR), Cuerpos Académicos de Neurociencias (UV-CA-28) y Neuroquímica (UV-CA-304).

Keywords: autism, cerebellum, GABA receptors, enriched environment.

Disclosures: **O. Cruz:** None. **L. García:** None. **G. Coria Avila:** None. **M. Toledo:** None. **M. Hernández:** None. **J. Manzo:** None.

Poster

030. Environmental and Immunological Influences on Autism

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Program #/Poster #: 030.09/A23

Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks Family Foundation
Robert E. Landreth and Dona Landreth Family Foundation
5T32GM008541

Title: Depletion and repopulation of microglia ameliorates maternal inflammation-induced neurobehavioral abnormalities and neurotogenic phenotype of microglia

Authors: *S. IKEZU¹, A. A. VAN ENO¹, H. YEH¹, M. WOODBURY¹, S. SIVAKUMARAN², C. HOLLAND², T. GUILLAMON-VIVANCOS², A. YOSHII-KITAHARA¹, Z. RUAN¹, J. DELPECH¹, P.-H. CHAO¹, M. B. BOTROS¹, A. DESANI¹, O. BUTOVSKY⁵, S. MANIMARAN³, W. E. JOHNSON³, M. MEDALLA², J. I. LUEBKE², T. IKEZU^{1,4}

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Abstract: Viral or bacterial infection during the first trimester of pregnancy has been associated with a higher incidence of Autism Spectrum Disorders (ASD) regardless of the pathogen, suggesting that the subsequent maternal and fetal innate immune response plays a critical role in the development of ASD. Neuroinflammation is one of the central features of ASD neuropathology. Significantly elevated microglial activation has been shown in the cortical, subcortical and cerebellar regions in postmortem ASD brains, and by live PET imaging of young adult subjects with ASD. RNA-sequencing studies of ASD patient brains further revealed an involvement of neuro-immune and microglial genes, supporting the notion that abnormally activated microglia may underlie ASD pathogenesis. However, it remains unknown how prenatally immune perturbed microglia are activated and whether activated microglia are directly involved in neurodevelopmental abnormalities or clinical symptoms of ASD. We hypothesize that prenatally immune perturbed microglia lead to development of aberrant neural circuits and mediate ASD-like abnormal behaviors. To test this hypothesis, we comprehensively characterized the role of microglia in the maternal immune activation (MIA) phenotype, which is widely used for investigating the ASD phenotype, under the colony stimulating factor 1 receptor inhibitor treatment for depletion and repopulation of microglia. First, pregnant females were injected with the viral mimic poly(I:C) at E9.5 and their offspring were tested for behavior abnormalities with or without drug treatment. Remarkably, increased repetitive behaviors and social deficits observed in MIA offspring were completely ameliorated by microglia depletion and repopulation. Next, we examined the morphology of dendritic spines on biocytin-filled and physiologically characterized intrinsically bursting (IB) pyramidal neurons of layer V (L5) in the medial prefrontal cortex (mPFC). We found that MIA increased the number of more plastic -thin and filopodia type- spines, an effect that was reversed by microglial depletion or repopulation. Moreover, our RNA sequence transcriptome of microglia purified from the MIA offspring have revealed that prenatally immune perturbed microglia secrete excessive cellular protrusion and neurotogenic factors, suggesting that a contribution of microglia to altered pyramidal cell spine morphology by MIA. Interestingly, aberrantly increased neurotogenic factors secreted from

microglia were also normalized by microglial repopulation, supporting the notion that these microglial molecules can be therapeutic targets for MIA mediated ASD-like behaviors.

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Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.10/A24

Topic: A.07. Developmental Disorders

Support: NIH RO1ES025549

Title: Combined environmental stressors as a mouse model of autism spectrum disorder: Sex-specific social behavior deficits and underlying neuro-immune mediators

Authors: ***K. E. MALACON**^{1,2}, **C. J. SMITH**², **S. D. BILBO**²

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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication, engagement in repetitive behaviors, and a sex bias in prevalence (higher in males). Air pollution is one of the most harmful environmental toxicants, and several epidemiological studies have linked prenatal air pollution exposure with an increased risk of ASD. Furthermore, studies have shown that maternal exposure to stressful life events during pregnancy increases the severity of ASD symptoms. Our lab has developed a maternal immune activation paradigm which combines diesel exhaust particles (DEP) with a maternal stressor (resource deprivation; MS). We hypothesized that DEP/MS exposure would induce ASD-relevant behavioral deficits in male offspring only. We assessed the behavior of DEP/MS-exposed or control-exposed mice on sociability, social novelty preference, marble burying, and open field assays during adolescence. We found that in males but not females, DEP/MS exposure significantly decreased preference for social vs. non-social stimuli, as reflected in both a decrease in social investigation and an increase in object investigation.

Similarly, while control males preferred to interact with a novel peer over their cage mate, DEP/MS males demonstrated the opposite preference (cage mate over a novel peer). DEP/MS exposure had no effect on marble burying behavior (a measure of repetitive behavior) or on activity in an open field in either sex. Microglia, the resident immune cells of the brain, are key regulators of the neural response to immune activation and appear to be chronically activated or altered in a significant subset of patients with ASD, making them good candidates for translating such environmental exposures into neural outcomes. We are currently investigating the impact of DEP/MS on the morphology of microglia in areas of the brain that are a) important for social behavior and b) implicated in ASD, such as the amygdala and cerebellum. Elucidating the impact of DEP/MS exposure on microglial structure and function will significantly advance our understanding of the sex-specific neuroimmune mechanisms underlying ASD.

Disclosures: **K.E. Malacon:** None. **C.J. Smith:** None. **S.D. Bilbo:** None.

Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.11/A25

Topic: A.07. Developmental Disorders

Support: NIH R01ES025549

Title: Combined environmental stressors as a mouse model of autism spectrum disorder: Sex-specific changes in the gut microbiome and intestinal epithelial barrier

Authors: ***C. J. SMITH**, K. E. MALACON, P. K. TRAN, S. D. BILBO
Lurie Ctr. for Autism, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Autism spectrum disorder (ASD) is characterized by impaired social interaction and communication, engagement in repetitive behaviors, and a sex bias in prevalence (higher in males). Importantly, alterations in the gut microbiome and intestinal epithelial barrier have also been reported in ASD and may contribute to behavioral deficits. Our lab has recently developed a novel mouse model of ASD in which pregnant C57Bl/6 mouse dams are exposed to a combination of diesel exhaust particles (DEP) and maternal stress (MS). Both of these exposures during pregnancy are associated with increased ASD risk in humans. Here, we show that DEP/MS exposure induces deficits in sociability, as well as social novelty preference, in male but not female offspring. Thus, we next hypothesized that DEP/MS exposure would induce sex-specific changes in the gut microbiome and intestinal epithelium. Our results show that DEP/MS exposure leads to age-specific changes in the gut microbiome, in males only. Specifically, we observed increased alpha diversity of the microbiome (diversity within an animal) at postnatal day (PND) 45, but decreased alpha diversity at PND60, in male offspring only. Similarly,

principle coordinates analysis (PCoA) revealed discrete clustering of DEP/MS vs. control males at PND60, but not PND45. No changes were observed in females. Finally, we found sex-specific changes in mRNA expression in the intestinal epithelium. In detail, in the small intestine, we found that, relative to control, DEP/MS exposure decreased (Ocln), zona occludens 1 (Zo1), and claudin 15 (Cl15) mRNA expression in males, but increased expression of these genes in females, at PND45. These genes transcribe proteins that are critical components of tight junctions in the epithelium, suggesting that DEP/MS exposure decreases the integrity of the epithelial barrier in males. Currently, we are investigating the neuro-immune mechanisms by which gut dysbiosis may causally contribute to social behavior deficits in this model of ASD.

Disclosures: C.J. Smith: None. K.E. Malacon: None. P.K. Tran: None. S.D. Bilbo: None.

Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.12/A26

Topic: A.07. Developmental Disorders

Title: Valproic acid inductions of NRF2 expression in fetal but not maternal brain: Support for the GABA shift hypothesis

Authors: *J. GIFFORD, S. A. NORTON, A. W. KUSNECOV, G. C. WAGNER
Psychology, Rutgers Univ., Piscataway, NJ

Abstract: The GABA-shift hypothesis proposes that GABA agonist action is excitatory early in development transitioning to inhibitory action later in life. The GABA agonist valproic acid (VPA; 300 mg/kg s.c.) was administered to pregnant C57 mice on embryonic day 13. Fetal and maternal brains were harvested two hours post VPA exposure and assayed for NRF2 and H3 expression through Western blot analysis. It was observed that NRF2 expression was increased in fetal, but not maternal tissue. Since NRF2 expression is activated by oxidative stress, these results are interpreted as supporting the GABA-shift hypothesis and that VPA exerts its developmental damage through excitotoxicity.

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Poster

030. Environmental and Immunological Influences on Autism

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Program #/Poster #: 030.13/A27

Topic: A.07. Developmental Disorders

Support: Department of Defense (AR130137)
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Title: Modulating the pathogenicity of maternal anti-Caspr2 antibody in ASD

Authors: *L. BRIMBERG¹, S. MADER³, D. COMOLETTI⁴, B. T. VOLPE⁵, B. DIAMOND²
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Abstract: The concept that the in utero environment, and specifically maternal antibodies, can contribute to the development of Autism spectrum disorders (ASD) has been entertained for over a decade. We have identified antibodies targeting the protein Caspr2 to be present in high frequency in mothers with an ASD child. We showed that a single exposure in utero to a monoclonal anti-Caspr2 antibody, derived from a mother of an ASD child, can lead to an ASD like phenotype in mice offspring. We have generated a new model where anti-Caspr2 antibodies are present during gestation in mice immunized with the extracellular portion of Caspr2. Male and not female fetuses of dams harboring anti-Caspr2 antibodies showed thinning of the cortical plate and reduced proliferating cells at gestational day E15.5 similar to our previous results in male fetuses exposed in utero to monoclonal anti-Caspr2 antibody. This histopathology was not seen in fetuses of control mice. Male mice exposed in utero to anti-Caspr2 antibodies showed repetitive/ stereotypic behavior; they buried significantly more marbles in the marble burying test, and spent more time grooming than control mice. They also showed impairment in novelty interest in the social preference test; they spent less time sniffing a novel mouse compared to a familiar mouse in the three chamber apparatus. Since it is our aim to protect pregnancies that are at risk, we have developed a decoy antigen by creating a fusion protein of the extracellular portion of Caspr2 and a mutated immunoglobulin Fc domain which we have determined does not cross the placenta, and therefore does not enter the fetal circulation. We demonstrated that the mutated Fc-Caspr2 can deplete anti-Caspr2 antibodies from serum of mice immunized with Caspr2 and from plasma of an ASD child who have Caspr2 plasma reactivity. Our preliminary findings also indicate that in vivo injection of the mutated Fc-Caspr2 to mice making high titers

of anti-Caspr2 antibody can reduce anti-Caspr2 titers with no obvious toxicity. Our approach could apply to many antibodies that potentially impair fetal development.

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Poster

030. Environmental and Immunological Influences on Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 030.14/A28

Topic: A.07. Developmental Disorders

Support: NEUROCHLORE

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Federation pour la Recherche sur le Cerveau
CIFRE-ANRT 2014-1056
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Fondation Bettancourt Schueller

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

Authors: *M. CHIESA¹, D. GUIMOND¹, R. TYZIO², A. PONS BENNACEUR², N. LOZOVAYA¹, N. BURNASHEV², D. C. FERRARI¹, Y. BEN-ARI¹

¹Neurochlore, Marseille, France; ²INMED UMR1249, Marseille, France

Abstract: Epidemiological studies have provided contradictory data on the deleterious sequels of cesarean section (C-section) delivery and their links with developmental brain disorders such as Autism Spectrum Disorders. To gain better insight on these issues, we have now compared physiological, morphological and behavioral parameters in vaginal, term and preterm C-section delivered mice. We report that C-section delivery does not lead to long-term behavioral alterations though preterm C-section delivery modifies communicative behaviors in pups. Moreover, C-section delivery neither alters the GABA developmental excitatory to inhibitory shift nor the frequency or amplitude of glutamatergic and GABAergic postsynaptic currents in hippocampal pyramidal neurons. However, these neurons present an underdeveloped dendritic arbor at birth in pups born by C-section delivery, but this difference disappears one day later suggesting an accelerated growth after birth. Therefore, C-section delivery, with prematurity as an aggravating factor, induces transient developmental delays but neither impacts the GABA developmental sequence nor lead to long-term consequences in mice. The deleterious sequels of C-section delivery described in epidemiological studies might be due to a perinatal insult that could be aggravated by C-section delivery.

Disclosures: **M. Chiesa:** A. Employment/Salary (full or part-time); NEUROCHLORE. **D. Guimond:** A. Employment/Salary (full or part-time); NEUROCHLORE. **R. Tyzio:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NEUROCHLORE. **A. Pons bennaceur:** None. **N. Lozovaya:** A. Employment/Salary (full or part-time); NEUROCHLORE. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NEUROCHLORE. **N. Burnashev:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NEUROCHLORE. **D.C. Ferrari:** A. Employment/Salary (full or part-time); NEUROCHLORE. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NEUROCHLORE. **Y. Ben-Ari:** A. Employment/Salary (full or part-time); NEUROCHLORE. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NEUROCHLORE.

Poster

030. Environmental and Immunological Influences on Autism

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Program #/Poster #: 030.15/A29

Topic: A.07. Developmental Disorders

Support: Japan Agency for Medical Research and Development (JP16gm0510008)
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John Mung Program from Kyoto University

Title: A potential blood-based DNA methylation biomarker for autism spectrum disorder

Authors: ***R. KIMURA**, Y. FUNABIKI, M. NAKATA, S. SUZUKI, T. AWAYA, T. MURAI, M. HAGIWARA
Kyoto Univ., Kyoto, Japan

Abstract: Increasing evidence suggests that epigenetic modifications, including DNA methylation, play a role in the etiology of Autism Spectrum Disorder (ASD). In this study, we sought to find a novel diagnostic biomarker for ASD using DNA methylation profiling from peripheral blood. We examined two independent cohorts, which were assessed for symptom severity of ASD. DNA methylation profiles were obtained using the HumanMethylation450K BeadChip array. Machine-learning techniques were applied to methylation data for classifying between individuals with ASD and controls. Pyrosequencing analysis was conducted to validate microarray results. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic accuracy of markers. Global DNA methylation was significantly different between ASD patients and controls. Our identified CpG site (cg20793532), which was annotated to the

PPP2R2C gene, showed the best performance in discrimination between ASD patients and controls using two types of algorithms. Pyrosequencing confirmed that this site was significantly hypermethylated in ASD patients than controls. The area under the curve (AUC) of ROC was 0.76 in the combined cohort. The methylation level of this site was correlated with ASD severity. This study revealed a novel potential biomarker for the ASD diagnosis. Our findings provide support for the development of DNA methylation as a promising ASD biomarker.

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Poster

030. Environmental and Immunological Influences on Autism

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Topic: A.07. Developmental Disorders

Support: DP2ES025453
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U2CES026561

Title: Assessing temporal patterns of inflammation associated with autism through the use of novel tooth-matrix biomarkers

Authors: ***E. BALDWIN**¹, **D. DUMITRIU**¹, **B. D. FREEMAN**², **V. NGUYEN**², **C. AUSTIN**², **S. NARASIMHAN**², **S. S. ANDRA**², **M. ARORA**²

¹Neurosci., ²Envrn. Med. & Publ. Hlth., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Autism spectrum disorder (ASD) is estimated to affect 1 in 59 children worldwide (CDC). Despite high prevalence, relatively little is known about the cause of this devastating disorder. While both genetic and environmental factors are known to play a role, the existence of discordance in monozygotic twins points to the complex interactions that mediate the development of ASD. For example, while certain maternal environmental exposures and maternal inflammatory conditions during pregnancy have both been tied to increased risk of autism, no single exposure is deterministic. Understanding the complex and temporally sequenced interplay between various intrinsic and extrinsic exposures might increase predictive power and offer hope for new preventative interventions. Most current methods of assessing exposures, such as using blood or urine samples, offer limited information since they assess only one or a few time points. However, the dentin in primary teeth acts as a biological hard drive that begins forming in utero, storing incremental snapshots of an individual's environment, akin to

developing tree-rings, and enabling the creation of a temporal map of exposures during key fetal and postnatal periods. Using this approach, our lab has previously shown slight but significant dysregulation of metals in monozygotic and dizygotic twins discordant for ASD at key developmental critical periods (Arora et al, Nature Communications 2017). Given known interplay between inflammation and metal uptake/metabolism, and the role of inflammation in increased risk of ASD, we are currently investigating whether the uncovered metal dysregulation is accompanied by slight differences in fetal and postnatal inflammation. Using a combination of novel immunohistochemical and proteomic techniques, we are currently screening a variety of inflammatory biomarkers, such as Hsp70, IL1Beta, cortisol and CRP, for their potential to be trapped in dentin with developmental specificity. Time-sequenced quantification will then be obtained from naturally shed teeth of ASD versus control cases, including discordant monozygotic and dizygotic twins using dating techniques previously described (Austin et al Scientific Reports 2016, Arora et al Nature Communication 2017). These data will uniquely offer an unprecedented look at how the temporal dynamics of pre- and post-natal inflammation contribute to the development of ASD.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 031.01/A31

Topic: A.07. Developmental Disorders

Support: EDA Rocket Fuel Fund grant (WSM)
NIH grant HD084953 (MER)
NARSAD Young Investigator Award (JLP)
BSF 2015255 (JLP)

Title: The selective M₁ muscarinic agonist CDD-0102A alleviates stereotyped motor behaviors and behavioral flexibility deficits in the BTBR mouse model of autism spectrum disorders

Authors: ***W. S. MESSER, JR**¹, G. A. JOB², E. M. PRAGER³, J. L. PLOTKIN³, M. E. RAGOZZINO²

¹Pharmacol., Univ. of Toledo, Toledo, OH; ²Psychology, Univ. of Illinois at Chicago, Chicago, IL; ³Dept. of Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY

Abstract: Autism spectrum disorders (ASD) are a set of neurodevelopmental disorders marked by a lack of social interaction, restrictive interests and repetitive behaviors. There is a paucity of pharmacological treatments to reduce core symptoms in ASD. Various lines of evidence indicate

that reduced brain muscarinic cholinergic receptor activity may contribute to an ASD phenotype. Therefore, the first set of experiments examined whether the partial M₁ muscarinic receptor agonist, CDD-0102A, alleviates stereotyped motor behaviors and/or behavioral flexibility deficits in the BTBR T+Itpr3^{fl}/J (BTBR) mouse model of autism as compared to C57BL/6J (B6) control mice. Male and female mice were tested in these experiments. There was no sex difference in either strain for behavioral measures or drug effects on behaviors. In Experiment 1, a change in the home environment (removal of nesting material) induced digging of home cage bedding. CDD-0102A (0.06, 0.12 or 0.30 mg/kg), administered intraperitoneally (ip) 30 minutes prior to testing, dose-dependently reduced digging behavior in both BTBR and B6 mice with significant decreases observed at both the 0.12 and 0.30 mg/kg doses in BTBR mice ($p < 0.01$). In Experiment 2, the effects of CDD-0102A (0.02, 0.06 or 0.12 mg/kg ip) were examined in a spatial reversal learning test using probabilistic reinforcement. CDD-0102A, injected 30 minutes prior to reversal learning, attenuated a probabilistic reversal learning deficit in BTBR mice in a dose-dependent fashion by significantly reducing regressive errors (at both the 0.06 and 0.12 mg/kg doses, $p < 0.01$). The behavioral data, particularly the decrease in regressive errors in BTBR mice, suggest an involvement of striatal M₁ muscarinic receptors in the beneficial effects of CDD-0102A. Since, within the striatum, M₁ muscarinic receptors are expressed exclusively in medium spiny neurons and D₂ medium spiny neurons/indirect pathway spiny projection neurons are associated with movement suppression, a separate set of studies focused on examining a possible mode of action. In Experiment 3, CDD-0102A dose-dependently increased dendritic excitability in indirect pathway medium spiny neurons following back propagation of single or theta burst trains of action potentials in mouse striatal slices, with significant effects observed at the highest concentration tested (1.0 mM). Taken together, the results suggest that treatment with a partial M₁ muscarinic receptor agonist may reduce repetitive behaviors and restricted interests in ASD, perhaps through altering dendritic excitability in indirect pathway medium spiny neurons.

Disclosures: W.S. Messer: Other; Patents related to the use of muscarinic agonists.. **G.A. Job:** None. **E.M. Prager:** None. **J.L. Plotkin:** None. **M.E. Ragozzino:** Other; Patents related to the use of muscarinic agonists..

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.02/A32

Topic: A.07. Developmental Disorders

Support: NIH Grant HD084953

Title: Glutamate efflux changes in the dorsolateral striatum of the BTBR mouse during stereotyped motor behavior: Modulation by M₁ muscarinic receptors

Authors: *M. E. RAGOZZINO¹, R. OCAMPO¹, P. TENEQEXHI¹, W. S. MESSER, JR²
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Abstract: Repetitive behaviors and restricted interests is one of the defining features in autism spectrum disorders (ASD). Preclinical studies indicate that the dorsolateral striatum is part of a larger neural system involved in the expression of stereotyped motor behaviors. Further, there is evidence that glutamate transmission is critical for the expression of stereotyped motor behaviors. Other findings indicate that activation of M₁ muscarinic receptors with the partial M₁ muscarinic receptor agonist, CDD-0102A, reduces stereotyped motor behaviors in the BTBR T+Itpr3^{tf}/J (BTBR) mouse model of autism. The present experiment determined whether glutamate efflux from the dorsolateral striatum in BTBR mice differentially changes during a stereotyped motor behavior (digging) compared to that of C57BL/6J (B6) control mice. The experiment further investigated whether treatment with CDD-0102A simultaneously modulated digging behavior and glutamate release. Prior to behavioral testing, an enzyme-based glutamate biosensor was inserted into the dorsolateral striatum of each mouse. After a four-hour equilibration period, each mouse was moved from its home cage to a new chamber with new bedding. Glutamate efflux was measured continuously for twenty minutes. Any period of 5 consecutive seconds or greater in which a mouse exhibited digging behavior was counted as a bout. Glutamate efflux during a digging bout did not change significantly from that of baseline levels in B6 mice. In contrast, glutamate efflux dropped by approximately 200 nM during a digging bout from that of baseline levels in BTBR mice. In BTBR mice, changes in dorsolateral striatal glutamate efflux during digging were not related to the bout duration. In addition, injection of CDD-0102A (0.12 mg/kg ip) in BTBR mice attenuated the reduction in glutamate efflux during digging behavior and overall reduced the number of digging bouts. The current findings suggest that glutamate transmission in the dorsolateral striatum is dysregulated in BTBR mice and may contribute to the elevated stereotyped motor behaviors. Moreover, activation of M₁ muscarinic receptors modulates glutamate signaling in the dorsolateral striatum by increasing glutamate levels during digging behavior. Overall, the results suggest that treatment with a partial M₁ muscarinic receptor agonist may alleviate repetitive behaviors and restricted interests in part by correcting glutamate signaling.

Disclosures: **M.E. Ragozzino:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds patent related to use of muscarinic agonists for the treatment of autism spectrum disorders. **R. Ocampo:** None. **P. Teneqexhi:** None. **W.S. Messer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds patent related to use of muscarinic agonists for the treatment of autism spectrum disorders.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.03/A33

Topic: A.07. Developmental Disorders

Support: Children's Tumor Foundation #2015-01-013 to LX
NIH Pioneer Award DP1ES024088 to MJZ
NIH Grant R01 NS031768 to WDS
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Title: Functions of Neurofibromin in cortical circuit development

Authors: *L. XING¹, M. J. ZYLKA^{1,2}, W. D. SNIDER¹

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Abstract: Neurofibromatosis Type 1 (NF-1) is an autosomal dominant inherited neurodevelopmental disorders affecting 1 in every 3000 individuals. NF-1 is caused by loss of function of the gene Neurofibromin (Nf1), which encodes a Ras GTPase-activating protein negatively regulating Ras activity and downstream signaling cascades, including the ERK/MAPK signaling pathway. Besides cutaneous manifestations, NF-1 patients frequently exhibit brain growth alterations, neurodevelopmental delay, learning deficits, motor deficits, and high prevalence of autism and seizures. However, molecular and cellular mechanisms underlying the pathogenesis of these central nervous system associated-neurological phenotypes in NF-1 are largely unknown. In this study, we investigated the effect of Nf1 loss-of function in the developing cortex by inactivating Nf1 in radial glial cells using an Emx:Cre line. We found that homozygous Nf1 conditional knock out (*Nf1^{loxp/loxp};Emx:Cre*) mice exhibit phenotypes similarly observed in human patients, suggesting *Nf1^{loxp/loxp};Emx:Cre* mice are valid models to investigate the function of Nf1 in cortical development and circuit formation. We found a significant increase in cortical thickness reminiscent of macrocephaly at postnatal day 14 in *Nf1^{loxp/loxp};Emx:Cre* mice. We found that the increase in cortical thickness is associated with overproduction of oligodendrocytes, rather than cortical principle neurons. On the contrary, neuronal numbers of upper layers (Layer 2-4) were significantly reduced due to the premature transition from neurogenesis to gliogenesis. While the cortical laminar structure was largely normal in mutant mice, we found the extension of long-range projecting axons in was drastically reduced, especially the corticospinal tract from cortical layer V neurons. Similar effect on corticospinal axon extension was recapitulated when ERK/MAPK was directly activated by a constitutive active form of Mek1. We then tested the layer V neuron-autonomous effect of Nf1 inactivation using a *Retinol binding protein 4:Cre (Rbp4:Cre)* line. We found that the spinal cord innervation of corticospinal axons was significantly reduced in lumbar segments of the spinal

cord in *Nf1^{loxp/loxp};Rbp4:Cre* mice. This results suggest that NF1-mediated regulation of ERK/MAPK signaling is critically required for the proper establishment of cortical long-range projections. Aberrant development of cortical long-range projections may contribute to neurobehavioral deficits in NF-1.

Disclosures: L. Xing: None. M.J. Zylka: None. W.D. Snider: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.04/A34

Topic: A.07. Developmental Disorders

Support: CIHR Grant MOP-142308

Title: Maternal postpartum SSRI influences offspring microbiome and neuroinflammation in a sex-specific manner

Authors: *W. QIU¹, K. GO², C. FERNANDO³, A. ALBERT⁴, J. E. HILL³, L. A. M. GALEA^{2,5}
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Abstract: Postpartum depression (PPD) affects 15% of mothers. Selective serotonin reuptake inhibitors (SSRIs) are prescribed to treat PPD. SSRI use during peripartum may be linked to increased Autism Spectrum Disorder (ASD) diagnoses in children. Studies have shown that certain bacteria within the gut can influence social and anxiety-like behaviour with similarities to those of ASD patients. Oxytocin (OT) is under investigation as a treatment for ASD, but OT is a large neuropeptide that has difficulty crossing the blood-brain barrier (BBB). TriozanTM is a nanoformulation that can facilitate OT to cross the BBB. Here, we hypothesize that in a rat model of PPD, maternal SSRI exposure will induce an ASD-like behaviour phenotype and dysbiosis within offspring animals, and OT treatment can negate the potential negative effects of maternal treatments. To simulate PPD and SSRI use dams were administered corticosterone and/or fluoxetine, a common SSRI, or vehicle during the postpartum. Offspring were then exposed to OT (0.5 mg/kg), OT+TriozanTM (0.25mg/mL; adjusted to 0.5mg/kg), or vehicle for 10 days (PD25-34). Stool samples were taken during offspring adulthood and we then performed chaperone-60 (CPN-60) sequencing of microbiome content. Offspring performed the 3-chambered social behaviour test and elevated-plus maze during adulthood. Preliminary data indicate an increase in the relative abundance of *Parabacteroides distasonis* and sex differences with fluoxetine treatment. In addition, maternal fluoxetine reduced levels of certain cytokines in

the hippocampus with some modulated differently by sex and offspring treatment. The results indicate that maternal fluoxetine exposure has long-lasting effects on offspring neuroinflammation, behaviour and microbiome.

Disclosures: W. Qiu: None. K. Go: None. C. Fernando: None. A. Albert: None. J.E. Hill: None. L.A.M. Galea: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.05/B1

Topic: A.07. Developmental Disorders

Support: MEXT Grant-in-Aid for Scientific Research on Innovative Areas “Adaptive Circuit Shift” 26112003 (H.O.)

JSPS Grant-in-Aid for Scientific Research 17K10090 (H.M.)

Title: Functional brain imaging in a mouse model of neurodevelopmental disorder

Authors: *H. MIZUMA¹, K. HIKISHIMA², N. HOSAKA¹, Y. MATSUMOTO¹, N. TAKATA³, H. ONOE⁴

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Abstract: A pregnant viral infection has been considered as one of the etiological factors of neurodevelopmental disorders in offspring. Indeed, maternal immune activation (MIA) by several pseudoviral infections in pregnant mice using polyinosinic:polycytidylic acid (poly(I:C)) elevated maternal blood cytokines including interleukin-6 and -17 and resulted in the incidence of abnormal offspring showing atypical cortical layer formations and autistic-like behaviors. Recently, Yim et al. have reported that the dysgranular zone of the primary somatosensory cortex (S1DZ) is a critical brain region for the behavioral abnormalities in offspring affected by MIA. However, the functional networks of SIDZ underlying cause of the behavioral phenotype in MIA offspring remained undetermined. To investigate the functional cortical interaction in the brain of MIA-affected offspring, we performed brain imaging study using ultra-high tesla (11.7T) magnetic resonance imaging (MRI) and positron emission tomography (PET) under the awake condition which we established previously. An MIA model was generated by intraperitoneal injection of Poly(I:C) (20 mg/kg) in pregnant mice on gestational day 12.5. The MIA-affected offspring showed a significant behavioral abnormality in the social approach test. A resting state functional MRI study revealed that MIA-affected offspring with social behavioral abnormality had higher functional connectivity with the ectorhinal and secondary motor cortices associated

with the S1DZ than those of the normal control. These changes in functional connectivities may play a crucial role in the appearance of the abnormal behaviors in the MIA offspring.

Disclosures: **H. Mizuma:** None. **K. Hikishima:** None. **N. Hosaka:** None. **Y. Matsumoto:** None. **N. Takata:** None. **H. Onoe:** None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.06/B2

Topic: A.07. Developmental Disorders

Support: Departmental Funds

Title: Brain-wide mapping of the developmentally regulated expression of the oxytocin receptor in mice

Authors: ***Z. T. NOLAN**

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Abstract: The endogenous neuropeptide oxytocin plays critical roles in the development and expression of social behavior. Impairment in oxytocin signaling has been implicated in neurodevelopmental disorders such as autism spectrum disorder. Interestingly, the oxytocin receptor (OTR) in neurons, the primary postsynaptic mediator of oxytocin signaling, undergoes dramatic changes in expression levels throughout development with the peak expression coinciding with a critical early social developmental period. Despite its potential significance, quantitative brain-wide spatial and temporal expression patterns of OTR remain largely unknown in developing postnatal brains. Furthermore, it remains unclear whether altered OTR signaling can affect the developmental expression pattern of OTR. To address this issue, we have examined the expression patterns of OTR positive cells throughout the whole brain at developmental time points (P7, P14, P21, P28) and in adulthood (P56) using transgenic reporter mice. These data were acquired using scanning serial two-photon tomography (STPT) and a data processing pipeline that allows us to map fluorescently labeled cells throughout the entire brain which can then be registered to standardized and age matched 3D brain atlases. First, we applied this methodology to the BAC generated OTR-eGFP mouse line to obtain the developmental trajectory of OTR neurons in OTR wild type brains. We observed differential peak expression moving from posterior to anterior cortex with overall peak at P14, which is consistent with previous reports. The spatial resolution of STPT allowed us to further identify smaller brain regions whose peak expression is not reached at P14. Second, we used OTR-Cre crossed with Ai14 to permanently label OTR neurons including neurons with developmentally transient expression. We found that decreased OTR expression in adulthood is driven by receptor

downregulation, not by cell death. Lastly, we quantified the OTR expression profile of the OTR hemizygous (OTR^{venus/wt}) mouse line that is known to display ASD-like social phenotypes including a lack of social preference. Interestingly, we found a significant delay in the peak expression of OTR throughout the cortex at P21. These data indicate that developmental changes in OTR gene expression take place in a region-specific manner and decreased level of OTR expression affects development of OTR expression. Future work with the OTR^{venus/wt} mice will aim to determine if manipulation of their altered OTR expression profile during development can impact their ASD-like social phenotype.

Disclosures: Z.T. Nolan: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.07/B3

Topic: A.07. Developmental Disorders

Support: MINECO Grant SAF2015-64163-R
NARSAD Grant 23663
MINECO Grant BES-2016-078420

Title: Abnormal developmental trajectory of ultrasonic vocalization emission pattern in Cntnap2 mice

Authors: *M. FERNANDEZ, T. SIERRA-ARREGUI, M. J. LARRAÑAGA, I. MOLLINEDO-GAJATE, O. PEÑAGARIKANO
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Abstract: The study of vocal communication in animal models provides key insight into the neurogenetic basis for speech and communication disorders. In humans, genetic variants in the CNTNAP2 gene have been associated with autism (a disorder with language and communication deficits), dyslexia, specific language impairment as well as with language development in the general population. Further, CNTNAP2 expression is known to be regulated by FOXP2, a transcription factor whose dysfunction is known to cause developmental speech and language disorder, indicating that they are part of a circuitry essential for human language. We have previously shown that a mouse model of autism, knockout for the Cntnap2 gene, displays abnormal vocal communication as shown by reduced number and altered pattern of syllable type when recording ultrasonic vocalizations (UsV) emitted by pups upon maternal separation at postnatal day (P) 7. UsV syllables are classified based on their sound frequency and duration, and the pattern of syllable type emission is believed to infer important information during vocal communication. Little is known about the normal developmental course of the pattern of UsV in

mice. In the present work we studied the developmental trajectory of UsV emitted by pups at P3, P6 and P9 in wild-type mice and *Cntnap2* mutants using the signal processing tool MUPET (mouse ultrasonic profile extraction). We obtained sound spectrographs (sonograms) showing the time/frequency representation of UsV emitted and we found interesting differences in the pattern of UsV emission among genotypes. Specifically, power spectral density (PSD) analysis for all UsV emitted showed that the Gaussian distribution of syllable frequency observed in wild-type is skewed to the left in knockouts, showing therefore a higher mean frequency, a difference that became more noticeable at developmental stage P6. Additional work is needed to provide more insight into the mechanistic contribution of *Cntnap2* in vocal communication

Disclosures: **M. Fernandez:** None. **T. Sierra-Arregui:** None. **M.J. Larrañaga:** None. **I. Mollinedo-Gajate:** None. **O. Peñagarikano:** None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.08/B4

Topic: A.07. Developmental Disorders

Support: Society of Obstetric Anesthesiology and Perinatology Gertie Marx research grant to C.P.

Title: Non-infectious fever in the near-term pregnant rat impairs social communication and behavior in the rat offspring

Authors: ***J. BOULANGER-BERTOLUS**¹, **I. ST CHARLES**¹, **S. SEGAL**², **C. J. WATSON**¹, **J. MARCHAND**³, **G. A. MASHOUR**¹, **C. PANCARO**¹

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Abstract: Fever during pregnancy has been shown to raise the risk of neurodevelopmental disorders such as autism spectrum disorder (ASD) in the offspring. Intra-partum fever occurs in up to 20% of women laboring under epidural anesthesia and has been associated with increased negative outcomes for the offspring (1). The majority of this fever is not associated with an infection but correlates with increased levels of interleukin 6 (IL-6), a proinflammatory cytokine (2). However, most of the preclinical and epidemiological work so far has focused on the consequences of infectious fever during pregnancy as opposed to intrapartum fever. To fill this gap in knowledge, previous work by our lab developed a model of noninfectious intra-partum fever by injecting near-term pregnant rats with increasing amounts of IL-6. We have shown that maternal IL-6 administration and accompanying fever causes neuroinflammation in the fetus (3). The current study expands these results by assessing the early behavioral outcomes of non-

infectious fever. Specifically, we investigated social communication and social behavior of the pups as early signs of neurodevelopmental disorders. Rat pups emit ultrasonic vocalizations when isolated from the dam and nest. These vocalizations have a mean frequency 40 or 66 kHz or are a composite of those frequencies and it has been suggested that they represent a communication of the emotional status of the pup (4). An elevation of the maternal temperature of 1 ± 0.2 °C shortly before birth impaired social communication by altering both the quantity and the quality of the ultrasonic vocalizations emitted by the pups: the total amount of USV emitted was decreased in the fever-exposed group compared to control pups ($t(99) = 2.08$, $p = 0.04$). This decrease affected in particular the 40-kHz USV ($t(99) = 2.20$, $p = 0.03$), and composite calls ($t(99) = 2.24$, $p = 0.02$), leaving the number of 66-kHz USV non-significantly changed ($t < 1$). On the other end, the frequency of the 66-kHz USV was increased in the experimental group compared to controls ($t(89) = 3.70$, $p < 0.001$), but not that of the 40kHz ($t < 1$). Furthermore, when tested for social behavior in a 3-chamber social test, pups prenatally exposed to maternal fever spent significantly less time exploring a stranger rat than control pups ($t(14) = 2.76$, $p = 0.015$). These results suggest that the induction of fever in the pregnant dam induces a modification of the vocal communication and social behaviors of the pups. Further work will assess to which extent these modifications model neurodevelopmental disorders such as ASD and aim at better understanding the neuronal mechanisms linking maternal fever and behavioral abnormalities in offspring.

Disclosures: J. Boulanger-Bertolus: None. I. St Charles: None. S. Segal: None. C.J. Watson: None. J. Marchand: None. G.A. Mashour: None. C. Pancaro: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.09/B5

Topic: A.07. Developmental Disorders

Support: ZIA MH000889
FRAXA Postdoctoral Fellowship

Title: Comparative findings: *In vivo* rates of cerebral protein synthesis in mouse models of neurodevelopmental disorders

Authors: *A. TOROSSIAN, R. M. SARÉ, T. HUANG, T. BURLIN, C. B. SMITH
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Abstract: Protein synthesis is necessary for cellular growth and maintenance and for many forms of neural plasticity. Mutations in genes involved in regulating protein synthesis are thought to be pathogenic in some neurodevelopmental disorders. In fragile X syndrome (FXS),

the leading genetic cause of intellectual disability, the *FMRI* gene is silenced by a repeat CGG expansion in the 5'-UTR and consequently its protein product, fragile X mental retardation protein (FMRP) is absent. FMRP is an RNA-binding protein that interacts with over 800 mRNAs and is thought to be involved in suppression of translation. The absence of FMRP in FXS is expected to result in an increased rate of protein synthesis. We have measured rates of cerebral protein synthesis (rCPS) *in vivo* in a mouse model of FXS (*Fmr1* knockout (KO)) and found increased rCPS in many brain regions (Qin et al., *J Neurosci* 25:5087, 2005). We have also studied another neurodevelopmental disorder, Tuberous Sclerosis Complex (TSC), in which intellectual disability, autism, and seizure disorders are primary symptoms. TSC is an autosomal dominant genetic disorder, characterized by mutations in either *TSC1* or *TSC2* that code for the proteins hamartin and tuberin, respectively. These proteins form a complex that inhibits mammalian target of rapamycin complex 1 (mTORC1), a key node in regulation of cell growth. In the absence of inhibition of mTORC1, we expected that protein synthesis rates would be elevated. In a mouse model of TSC, *Tsc2*^{+/-}, we measured rCPS *in vivo* and found that, contrary to our expectations, rates were decreased throughout the brain (Saré et al., *J Neurochem* doi.org/10.1111/jnc.14311). In this present study we report confirmation and expansion of these results in a TSC mouse model. We quantified rCPS *in vivo* in intact brains in awake WT (n=6) and *Tsc2*^{+/-} (n=4) adult male mice on a mixed background (B6;129S4). As in the previous study, we used the quantitative autoradiographic L-[1-¹⁴C]leucine method. Mice were implanted with catheters under isoflurane anesthesia 24 h prior to measurement of rCPS. The measurement was initiated by an intravenous injection of 100µCi/kg of L-[1-¹⁴C]leucine. Timed arterial plasma samples were drawn and analyzed for the 60 min time course of the specific activity of [¹⁴C]leucine. We analyzed 18 brain regions with the quantitative autoradiographic technique. Our results confirm our previously reported findings in TSC that rCPS were decreased throughout the brain. These findings emphasize the importance of regulation of protein synthesis in brain for normal function; dysregulation in either direction can produce serious consequences.

Disclosures: R.M. Saré: None. T. Huang: None. T. Burlin: None. C.B. Smith: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.10/B6

Topic: A.07. Developmental Disorders

Support: IBS-R002-D1

Title: SALM1 mutant mice display suppressed synaptic plasticity and inhibitory synapse development and abnormal social communication and startle response

Authors: *R. KIM¹, Y. LI, 305-701², E. KIM³

¹KAIST, Taejon-City, Korea, Republic of; ²IBS, Daejeon, Korea, Republic of; ³Inst. for Basic Sci. (IBS), Korea Adv Inst. Sci. & Tech. (KAIST), Daejeon, Korea, Republic of

Abstract: *Lrfn2*-mutant mice display suppressed synaptic plasticity and inhibitory synapse development and abnormal social communication and startle response

SALM1, also known as LRFN2, is a PSD-95-interacting synaptic adhesion molecule implicated in the regulation of NMDA receptor (NMDAR) clustering largely based on in vitro data.

However, its in vivo functions remain unclear. Here, we found that mice lacking

SALM1/LRFN2 (*Lrfn2*^{-/-} mice) show altered excitatory synaptic function, including enhanced NMDAR-dependent synaptic transmission but suppressed NMDAR-dependent synaptic

plasticity in the hippocampal CA1 region. Unexpectedly, SALM1 is expressed in both glutamatergic and GABAergic neurons, and *Lrfn2*^{-/-} CA1 pyramidal neurons show decreases in the frequency of spontaneous inhibitory synaptic transmission and density of inhibitory synapses.

Behaviorally, ultrasonic vocalization was suppressed in *Lrfn2*^{-/-} pups separated from their mothers, and acoustic startle was enhanced, but locomotion, social interaction, repetitive

behaviors, anxiety-like behavior and learning and memory were largely normal in adult *Lrfn2*^{-/-}

mice. These results suggest that SALM1/LRFN2 regulates excitatory synapse function,

inhibitory synapse development, and social communication and startle behaviors in mice.

Disclosures: R. Kim: None. Y. Li: None. E. Kim: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.11/B7

Topic: A.07. Developmental Disorders

Support: IBS-R0002-D1

Title: NGL-3 in the regulation of brain development, synaptic NMDAR function, and locomotive behaviors

Authors: *W. SHIN¹, H. LEE², K. KIM¹, E. KIM³

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Abstract: NGL-3 is a postsynaptic adhesion molecule known to directly interact with the excitatory postsynaptic scaffolding protein PSD-95 and trans-synaptically with LAR family receptor tyrosine phosphatases to regulate presynaptic differentiation. Although NGL-3 has been

implicated in the regulation of excitatory synapse development by in vitro studies, whether it regulates synapse development or function, or any other features of brain development and function, is not known. Here we report that mice lacking NGL-3 (*Ngl3*^{-/-} mice) show markedly suppressed normal brain development and postnatal survival and growth. A change of the genetic background of the mice from pure to hybrid one minimized these developmental effects but substantially suppressed NMDA receptor (NMDAR)-mediated synaptic transmission without affecting synapse development, AMPA receptor-mediated basal transmission, and presynaptic release. In mechanistic support of this NMDAR phenotype, NGL-3 could interact with subunits of NMDARs through extracellular domains, in addition to the predicted indirect mechanisms involving PSD-95. *Ngl3*^{-/-} mice displayed several behavioral abnormalities, including hyperactivity, anxiolytic-like behavior, impaired spatial memory, and enhanced seizure susceptibility. Among them, the hyperactivity was rapidly improved by the treatment with an NMDAR agonist. These results suggest that NGL-3 regulates brain development, synaptic NMDAR function, and locomotive and cognitive behaviors.

Disclosures: W. Shin: None. H. Lee: None. K. Kim: None. E. Kim: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.12/B8

Topic: A.07. Developmental Disorders

Support: IBS-R002-D1

Title: Layer 6 of the medial prefrontal cortex modulates prepulse inhibition via dorsomedial thalamus

Authors: *Y. KIM, J. KIM, E. KIM
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Abstract: Decreased prepulse inhibition (PPI) is one of characteristic phenomena in neuropsychiatric disorders such as schizophrenia, panic disorder, schizotypal personality disorder, Huntington's disorder, Fragile X syndrome, Tourette's syndrome, and obsessive-compulsive disorder. Dopaminergic receptor agonist and NMDA receptor antagonist can decrease PPI in both human and rodent studies. Additionally, many brain regions are related to including the medial prefrontal cortex (mPFC), dorsal and ventral striatum, amygdala, dorsomedial thalamus (DMT), globus pallidus, habenula, and ventral tegmental area. But it remains which brain region is critical for rescue of decreased PPI in animal model of neuropsychiatric disorders. Here we show that cortical layer VI specific IRSp53 deleted mice had decreased PPI as whole cortical layer specific IRSp53 deleted mice. Decreased PPI in these

mice can be rescued by haloperidol, D2 dopamine receptor antagonist. Electrophysiological study was measured as decreased synaptic transmission in mPFC and increased synaptic transmission in DMT, which brain region receives projections from layer VI of mPFC. Thus, we hypothesize that layer VI of mPFC modulates PPI via DMT. And our future plan is identifying the mechanism of haloperidol effect in rescue of PPI as well as restoring PPI using certain brain circuit between layer VI of mPFC and DMT.

Disclosures: Y. Kim: None. J. Kim: None. E. Kim: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.13/B9

Topic: A.07. Developmental Disorders

Support: UC Davis CTSC Pilot Award
NARSAD Young Investigator Grant
NIH 1R21MH116681-01

Title: Alterations in mouse cortical development following mid-gestational Poly(I:C)-mediated maternal immune activation

Authors: *C. P. CANALES¹, M. ESTES², I. ZDILAR¹, L. SU-FEHER¹, D. VAN DER LIST¹, S. CAMERON¹, J. P. ABOUBECHARA¹, R. CATTAPRETA¹, K. LIM¹, T. STRADLEIGH¹, L. HAAPANEN³, K. FARRELLY¹, J. VAN DE WATER³, A. K. MCALLISTER¹, A. S. NORD¹
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Abstract: Maternal immune activation (MIA) has emerged as risk factor for neurodevelopmental disorders (NDDs), including autism and schizophrenia. Animal models of MIA provide the opportunity to identify the molecular signaling pathways that initiate the disease process and lead to NDD-related neuropathology and behavioral deficits. We applied transcriptional and epigenomic profiling to identify changes in fetal mouse cortex across a time course following mid-gestational MIA via maternal poly(I:C) injection at E12.5. In order to reduce variability in the experimental model, we determined the effective dose of Poly(I:C) to induce reproducible levels of MIA and disease-relevant changes in offspring. Mice were bred and then injected with saline or poly(I:C). Cortex was dissected from E12.5, E14.5, E17.5 and P0 from MIA and control offspring and then processed for RNA-seq. We identified strong transient transcriptional signatures in fetal cortex. Via co-expression, several waves of changes in gene expression were identified following the maternal immune challenge. These changes included an initial acute signature suggesting activation of stress response pathways in the fetal brain,

followed by alterations to proliferation and neuronal differentiation that emerged at E14.5 and peaked at E17.5. In our initial datasets, MIA-associated transcriptional changes largely resolved or were too variable to be robustly identified by birth (P0). To validate transcriptional signatures, we used immunohistochemistry at E17.5, examining a number of candidates involved in different processes. We found anatomical and protein expression changes in E17.5 cerebral cortex concordant with signatures present in the RNA data, including reduced proliferative populations and altered cortical lamination patterns, but no evidence of previously reported focal dysplasia. In summary, the time-resolved transcriptomic maps provide novel insights into the molecular and developmental pathologies linking MIA and neurodevelopmental sequelae.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.14/B10

Topic: A.07. Developmental Disorders

Title: Principal component analysis (PCA) based data fusion approach for a mouse model of CLN6 Batten disease

Authors: T. BRAGGE¹, T. HUHTALA¹, *J. T. PUOLIVALI¹, J. BRUDVIG², T. JOHNSON², D. TIMM³, J. RYTKÖNEN¹, J. M. WEIMER⁴, A. J. NURMI¹, K. LEHTIMÄKI¹

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Abstract: The *Cln6^{nc1f}* mouse model has been characterized as a progressive animal model of CLN6 Batten Disease. Here, we characterize the *Cln6^{nc1f}* model from 3 to 12 months of age with a multimodal approach, combining advanced technologies such as kinematic gait analysis, MR based imaging techniques (T2, DTI), spectroscopy (1H-MRS), and metabolic profiling (FDG PET). Our data reveal the distinctly progressive nature of this genetic model both at functional (behavior) and pathological level, where the majority of readouts suggest clear connections between structure and function. However, individual phenotypic results and the time course of their development do capture quantitative connections between the various pathologies. Therefore, we use a PCA based approach to look at all measured variables together aiming to identify which readouts are connected in a consistent manner, and further, which combination of readouts best captures the progressive nature of the disease.

We used imaging, spectroscopic, and behavioral data collected from the same *Cln6^{nc1f}* and wild

type littermate controls (pooled and genders separated) at 3, 6, 9 and 12 months of age. The data reduction and fusion was performed in two phases: first, PCA was applied separately to normalized parameter data from each modality. Then, the first phase PC scores were transformed into final scores using contrastive PCA (cPCA).

The first identified component (cPC1) reveals progressively increasing genotype differences, consistently in both genders, reflecting decreases in structural brain volume, decreases in overall mobility, metabolic changes, and demyelination, especially in deep white matter structures. The second component (cPC2), consisting mainly of relative volumetric and metabolic changes between brain regions, was found to be gender dependent in *Cln6^{nclf}* mice.

Taken together, this data and analysis approach provides detailed insight on the key features of the *Cln6^{nclf}* phenotype and demonstrates how structural and functional readouts are connected using unbiased modeling.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.15/B11

Topic: A.07. Developmental Disorders

Support: NIH P50 MH106438

Simons Foundation (SFARI #321998)

Title: Synaptic and immune molecule expression in the developing brain in a mouse and non-human primate model of maternal immune activation

Authors: *S. CAMERON¹, M. ESTES¹, J. P. ABOUBECHARA¹, M. GANDAL⁵, D. VAN DER LIST¹, K. FARRELLY¹, A. MARTINEZ-HORTA¹, G. KINCHELOE¹, J. MACMAHON¹, L. HAAPANEN², J. VAN DE WATER^{2,3}, C. S. CARTER^{1,4}, C. M. SCHUMANN^{3,4}, M. D. BAUMAN^{3,4}, D. GESCHWIND⁵, A. K. MCALLISTER¹

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Abstract: Increasing evidence points to a central role for immune-related genes and immune responses to environmental stimuli in several neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD) and schizophrenia (SZ). Maternal infection during gestation, in particular, is a risk factor for both disorders. Mouse and non-human primate (NHP) models of maternal infection have strengthened the link between maternal immune activation (MIA) and

NDDs. Results from these studies have converged on the hypothesis that immune dysregulation from genetic or environmental risk factors alters immune molecules in the brain, changing synaptic connectivity, and leading to aberrant behaviors.

In order to test this hypothesis, we used poly(I:C) injection during gestation to mimic viral infection. Mice were injected with poly(I:C) at gestational day (GD) 12.5 and NHPs were injected with polyICLC at GD 43, 44 46 or 100,102,104. Behavioral abnormalities were confirmed in MIA offspring in both models. Subsequently, brain tissue (frontal cortex; FC, and hippocampus, HC) was collected from mice at birth (postnatal day 0; P0), P14, P30, P60, and P120. FC and HC from NHPs was collected at approximately 3.5 years. RT-PCR, RNAseq, and Western blotting was then used to study changes in expression of immune and synaptic molecules in the brains of offspring. RT-PCR and Western blotting indicate that several classes of immune molecules, including cytokines, their receptors and downstream signaling molecules, are altered in the brains of offspring from the MIA mouse model during development. RT-PCR indicates that cytokine receptor expression is significantly altered in an age-specific manner in FC in the mouse model. Across ages, the direction of change of cytokine receptors in MIA offspring shows an oscillating pattern—down at birth, up at P7, and down at P14—as compared to control offspring. This pattern of change is distinct from the protein levels of corresponding cytokines identified in our previous study (Garay et al.2013). Taken together, these findings demonstrate that MIA induces chronic changes in cytokine signaling in the frontal cortex of offspring. Ongoing studies are examining whether these MIA-induced changes in immune molecules can be replicated using RNAseq and validated at the protein level in the mouse model, whether they also occur in the NHP model, and whether they precede or follow changes in expression of synaptic proteins within a given brain region. Our results will indicate whether there may be a common immune and/or synaptic signaling pathway downstream of MIA in such disparate species as mice and NHPs.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.16/B12

Topic: A.07. Developmental Disorders

Support: R37NS031348

Title: Mice with a heterozygous missense mutation in *Gnb1* (*Gnb1*^{K78R/+}) exhibit developmental delay, hypoactivity, gait abnormality, and deficits in spatial learning

Authors: *M. YANG^{1,2}, S. COLOMBO¹, E. OZURUONYE^{1,2}, S. OWENS^{1,2}, G. MONTERO¹, S. PETRI¹, W. N. FRANKEL^{1,3}, M. BOLAND^{1,4}, D. GOLDSTEIN^{1,3}

¹Inst. for Genomic Med., ²Mouse NeuroBehavior Core, ³Dept. of Genet. and Develop., ⁴Dept. of Neurol., Columbia Univ. Med. Ctr., New York, NY

Abstract: *GNBI* encodes the G protein beta 1 subunit of heterotrimeric G proteins mediating G protein-coupled signaling. Our group recently linked *GNBI* germline mutations to a neurodevelopmental disorder characterized by developmental delay, muscle tone and ophthalmological defects as well as a variety of seizures. Mice heterozygous for the K78R missense mutation in *Gnb1* were generated by CRISPR/Cas9 and tested in our new Mouse NeuroBehavior Core, for phenotypes relevant to the neurodevelopmental disorder, with a battery of tests including ultrasonic vocalizations in pups, open field activity, gait, fear conditioning, and Morris water maze. *Gnb1*^{K78R/+} pups exhibited developmental delays in the first two postnatal weeks, as observed by reduced separation-induced ultrasonic vocalizations, reduced body weight, and impaired righting reflex and sensory-motor reflex. Adult *Gnb1*^{K78R/+} mice exhibited a marked reduction in locomotor activity in the open field test, and this hypoactivity is not attributable to differences in anxiety. In-depth analysis of motor phenotypes using the Catwalk assay indicated that *Gnb1*^{K78R/+} mice walk in a “hunchback” manner, with reduced foot print size and shortened print position (the distance between the placement of front and hind paws over one walking step). To investigate phenotypes that might be relevant to intellectual delays found in patients with *GNBI* mutations, we are currently conducting a battery of learning and memory tests. Preliminary results indicate normal fear conditioning but impaired spatial learning in *Gnb1*^{K78R/+} mice. Control parameters (swim speed and swim distance) ruled out swimming deficits as a contributing factor to the spatial learning deficit. We are in the early stage of testing complex cognitive performance in the Bussey-Saksida touchscreen chambers in adult mice. Of note, *Gnb1*^{K78R/+} mice experience thousands of spike-wave discharges (SWDs) a day, likely absence seizures, which could contribute to behavioral deficits. Taken together, our data suggest a salient role of *Gnb1* in early postnatal development, motor functions, and certain aspects of learning memory. Present data demonstrate that the K78R mouse model phenocopies many aspects of the neurodevelopmental disorder, allowing for further analysis of the neuronal defects underlying the disorder and for developing treatment strategies.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.17/B13

Topic: A.07. Developmental Disorders

Title: Longitudinal characterization of the *Cln6^{nclf}* mouse model of CLN6 Batten disease - Characterization of fine motor performance, brain pathology and metabolic changes

Authors: *M. VIHMA¹, K. LEHTIMÄKI¹, T. BRAGGE¹, T. HUHTALA¹, J. BRUDVIG², T. JOHNSON², D. TIMM³, J. T. PUOLIVALI¹, J. RYTKÖNEN¹, P. POUTIAINEN⁵, J. M. WEIMER⁴, A. J. NURMI¹

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Abstract: Batten's disease is defined as a broad group of rare genetic lysosomal storage diseases, referred to as neuronal ceroid lipofuscinoses (NCLs). CLN6 Batten Disease is a progressive rare disease characterized by neurodegeneration, motor and cognitive impairments, and the accumulation of autofluorescent storage material in lysosomes. The *Cln6^{nclf}* mouse model has been behaviorally and histologically characterized, but detailed imaging based structural and metabolic phenotypes and fine motor properties of the model have not been assessed. Such approaches are highly translationally relevant, closely resembling clinical situations where patients are evaluated repeatedly during the course of their disease. We used a longitudinal (3-12 months) and multimodal approach to assess key features of *Cln6^{nclf}* model over time: fine motor kinematic gait analysis for assessment of detailed motor phenotypes, anatomical and white matter imaging of the CNS by T2-MRI and DTI-MRI, respectively, metabolic profiling of the brain with PET imaging for glucose utilization and 1H-spectroscopy (1H-MRS) for key cellular metabolites.

Fine motor kinematic analysis revealed profound and progressive differences between WT and *Cln6^{nclf}* mice. There were also differences between genders in motor phenotype progression. Brain structural analysis revealed progressive atrophy including decreases in whole brain, striatal and cortical volumes in *Cln6^{nclf}* mice in both genders. However, inconsistencies in lateral ventricle volume development between genders in *Cln6^{nclf}* mice was observed. White matter imaging revealed progressively decreasing fractional anisotropy (FA), predominantly in deep white matter structures. 1H-MRS revealed consistent changes between genders in glutamine (GLN) and N-acetyl aspartate (NAA) levels, although many other metabolites were significantly altered at certain time-points. PET imaging revealed significant decreases in glucose uptake in *Cln6^{nclf}* mice at 12 months of age.

Taken together, this multimodal approach reveals distinct features of the *Cln6^{nclf}* model that have

not been previously described. This data may be useful in designing more sensitive pre-clinical studies for therapeutic development.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 031.18/B14

Topic: A.07. Developmental Disorders

Support: NIH Grant 5TL1TR001875-02
Robbins Family Fund GT006038

Title: Transcriptomic effects and neurological phenotypes in a mouse model of HNRNPU haploinsufficiency

Authors: *S. A. DUGGER^{1,2}, R. DHINDSA¹, M. HALVORSEN¹, S. OWENS¹, E. OZURUONYE¹, G. MONTERO¹, M. SAH¹, S. COLOMBO¹, S. PETRI¹, M. YANG¹, W. FRANKEL^{1,2}, M. BOLAND^{1,3}, D. GOLDSTEIN^{1,2}

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Abstract: Mutation of proteins that cause transcriptional dysregulation, such as RNA-binding proteins (RNABPs) and chromatin-modifying enzymes, are a well-described cause of neurodevelopmental syndromes such as autism and epilepsy. Copy number and single nucleotide variants of *HNRNPU*, which encodes the heterogeneous nuclear ribonuclear protein U have recently been implicated in a neurodevelopmental syndrome with several phenotypes of varying severity, but most commonly associated with epileptic encephalopathy. Although HNRNPU is a highly-abundant and ubiquitously-expressed ribonuclear protein involved in a variety of important nuclear processes such as DNA repair, mitosis, X-chromosome inactivation and regulation of gene expression, the role HNRNPU plays in neurological disease is unclear. Using a heterozygous *HNRNPU* knockout mouse model (*HNRNPU*^{+/-}), we assessed both the electrophysiological and transcriptional consequences of *HNRNPU* haploinsufficiency. *HNRNPU*^{+/-} mice demonstrate evidence of global developmental delay, with an early-onset, yet persistent, growth impairment and striking defects in isolated pup calls as determined by bioacoustic analysis of ultrasonic vocalizations. Surprisingly *HNRNPU*^{+/-} mice do not display overt spontaneous seizures; however, electroconvulsive threshold studies performed on male and female *HNRNPU*^{+/-} and *HNRNPU*^{+/+} littermates while blinded to genotype revealed a

significantly lower threshold to induction of maximal seizures. Furthermore, *HNRNPU*^{+/-} neural networks show evoked phenotypes reminiscent of defective inhibition. Comprehensive transcriptomic analyses performed on postnatal day 0 (P0) *HNRNPU*^{+/-} and *HNRNPU*^{+/+} cerebral cortices revealed 558 statistically differentially-expressed genes. Interestingly, approximately 60% of these genes found to be downregulated in expression are enriched for known epilepsy and developmental delay genes, and were overrepresented in various neuronal pathways including neurite outgrowth and synaptic organization, suggesting that HNRNPU is important in maintaining steady-state levels of important neuronal genes. Current efforts investigating these genes and pathways in the context of *HNRNPU* haploinsufficiency are ongoing. Overall, these data further highlight the neurodevelopment effects of heterozygous loss of *HNRNPU* and support the notion of transcriptional dysregulation as a contributing pathological factor to the diverse etiology of epileptic encephalopathy.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 031.19/B15

Topic: A.07. Developmental Disorders

Support: NIH P50 MH106438
Simons Foundation (SFARI #321998)

Title: Baseline immune response and poly(I:C) dose interact to cause behavioral and biological phenotypes in offspring following maternal immune activation

Authors: K. E. PRENDERGAST¹, M. ESTES¹, K. FARRELLY¹, D. VAN DER LIST¹, S. A. CAMERON¹, J. P. ABOUBECHARA¹, A. M. HORTA¹, G. KINCHELOE¹, J. MACMAHON¹, L. HAAPANEN², M. D. BAUMAN⁴, C. S. CARTER³, J. VAN DE WATER², *A. K. MCALLISTER¹

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Abstract: Viral infections during pregnancy are associated with increased risk of psychiatric disorders in offspring and the viral mimic, poly(I:C), is often used in mouse models of maternal immune activation (MIA). The poly(I:C) MIA model was originally designed to cause elevations in interleukin-6 (IL-6) in maternal serum to levels comparable to those induced by influenza.

Previously, we demonstrated that most of the available sources of poly(I:C) elicited an IL-6 response in pregnant mice that ranged from no difference compared to saline injections to a maximum increase of only 2% of the originally reported MIA values. Here, we show that the appropriate dose of any type, source, and lot of poly(I:C) necessary to cause reproducible and robust biological and behavioral phenotypes in offspring can be determined using sickness behaviors in the dam as well as measures of maternal IL-6. Importantly, low doses of poly(I:C), or high doses of less immunogenic forms of poly(I:C), can cause significant increases in maternal IL-6 that do not cross the threshold required for reproducible phenotypes in offspring. Moreover, the dose of poly(I:C) interacts with the baseline immune responsiveness (BIR) of the dam to cause phenotypes in offspring. First, we discovered that the BIR of virgin female mice from the same strain from the same vendor have a wide range of BIR, as measured by elevations in serum IL-6 following injection with a low dose (4mg/kg) of poly(I:C). Then, mice were divided into three BIR groups: low (bottom 25% of serum IL-6 response), medium (middle 50%) and high (top 25%) and each group was mated and then injected with a range of poly(I:C) doses in mid-gestation (E12.5). Young adult (P60) MIA offspring consistently showed increased repetitive grooming with the effects dependent on both polyI:C dose and BIR of the dams. For the lot of pure poly(I:C) that we used, altered behaviors were not present at the typically used dose of 20mg/kg in any BIR group, but appeared at 30mg/kg, and were less robust at the higher 40mg/kg dose. This U-shaped response curve is also present for BIR groups: there is a selective increase in repetitive grooming in MIA offspring from dams in the medium BIR at 30mg/kg and from the low BIR group at 40mg/kg, but no changes in the high BIR groups at either dose. Thus, BIR in females prior to pregnancy predicts the susceptibility or resilience of subsequent pregnancies to the effects of MIA. Efforts are ongoing to determine if these high levels of MIA elicit a distinct combination of phenotypes in offspring compared to intermediate levels of MIA, similar to what might be predicted from the wide range of psychiatric illnesses that result from maternal infection in humans.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 031.20/B16

Topic: A.07. Developmental Disorders

Support: NIH Grant MH091451
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Title: Developmental regulation of threat, dopamine and VTA-amygdala connectivity

Authors: *P. A. ROBINSON-DRUMMER¹, M. OPENDAK², R. M. SULLIVAN³

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Abstract: Emotional regulation is organized during early life and programmed through maternal regulation of infant behavior and physiology. This regulation system is active during ongoing mother-infant interactions but is most salient when the infant experiences a threat, such as a painful stimulus, with caregiver presence reducing stress hormones and distress. More recent research indicates that maternal regulation of the infant extends to the brain, although the neurobiology and mechanisms are largely unknown. Here we use infant rats' learning about threat with and without maternal presence. We question the role of amygdala nuclei, and their modulation by dopamine (DA) and its source, the ventral tegmental area (VTA). Infant rats were given paired novel (conditioned stimulus; CS) odor-0.5mA shock conditioning either in the presence of the mother or alone. Prior to conditioning, a portion of the pups were injected with ¹⁴C 2-DG (20mCi/100g, s.c). Immediately following conditioning, pup brains were removed, and stored at -80 C before being sectioned on a cryostat. The remaining littermates were tested 24 hr later on a Y maze. Our results indicate that odor-shock conditioning produced learning in pups as indicated by avoidance of the CS in the Y-maze. However, maternal presence during learning blocked pup learning such that CS avoidance did not differ from chance in pups conditioned with their mothers. Neural activity analyses indicate that learning- induced increases in the basolateral (BLA) and dorsolateral (LaDI) amygdala nuclei activity that was significantly reduced by maternal presence. A similar pattern was observed in the source of amygdala dopamine, the VTA. In a separate group of pups, amygdala microdialysis during conditioning revealed that shock decreased DA while maternal presence increased DA. Western blot analysis revealed conditioning in maternal presence also modulated Dopamine D1 receptors. These results extend previous reports by indicating a modulation of VTA activity by maternal presence that regulates amygdala dopaminergic activity. These results suggest that maternal regulation of the infant brain involves modulation of the pups' dopamine system by the mother.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.21/B17

Topic: A.07. Developmental Disorders

Title: Fine motor performance, brain volumetry and metabolism in *Cln2*^{R207X/R207X} nonsense point mutation model for CLN2 Batten disease

Authors: K. LEHTIMÄKI¹, T. BRAGGE¹, J. BRUDVIG², T. JOHNSON², D. TIMM², *A. J. NURMI¹, J. WEIMER², J. T. PUOLIVALI¹

¹Charles River Discovery, Kuopio, Finland; ²Sanford Res., Sioux Falls, SD

Abstract: The *Cln2*^{R207X/R207X} nonsense point mutation mouse model for CLN2 Batten Disease was recently developed to facilitate the development of mutation guided therapies. This model presents with brain gliosis, lysosomal accumulation of autofluorescent storage material and mitochondrial ATP synthase unit c, and significantly decreased activity of the *Cln2* protein product Tripeptidyl peptidase 1 (TPP1). The behavioral phenotype of the *Cln2*^{R207X/R207X} model has been shown to involve hyperactivity, tremors, and deficits in the coordinated motor tasks. However, brain structural volumetry, metabolic parameters, and fine motor performance have not been characterized. To strengthen the phenotypic description, we studied *Cln2*^{R207X/R207X} mice for their performance in highly sensitive motor gait analysis, brain volumetry by T2-MRI and neurometabolites of prefrontal cortex (PFC) using proton spectroscopy (1H-MRS). Data were collected from *Cln2*^{R207X/R207X} and WT mice at 2 and 3 months of age, until humane end point criteria were met. Brain volumetric data revealed significantly smaller whole brain volumes at both time-points in *Cln2*^{R207X/R207X} mice. Analysis by sexes revealed a major contribution coming from females, with males unaffected. Cortical volumes were decreased at 3 months, and female *Cln2*^{R207X/R207X} mice also showed decreased striatal and hippocampal volumes. ¹H-MRS analysis revealed that several metabolites were altered between time-points or sexes, warranting individual analysis of their relevance. The most consistent changes, occurring at both time-points and sexes, were glutamine increases and choline decreases. At 3 months, total creatines or sum of glutamate and glutamine were not affected, but glutamine/glutamate and creatine/phosphocreatine ratios were altered to a highly significant degree. While both changes require further studies, they open interesting research questions on glutamate-glutamine cycling and mitochondrial energy metabolism in this model. Kinematic analysis revealed clear overall motor phenotypes for pooled and individual sexes. Gait parameters for males were significantly different from WT at both 2 and 3 months of age, while females showed clear overall phenotype changes only at 3 months of age. Detailed analysis revealed gait parameters such as forelimb swing trajectory, lowered body posture and decreased diagonal gait mode as pronounced features in studied model.

Taken together, the data and analysis approach shown here provides further insight on the key features of the *Cln2*^{R207X/R207X} model ranging from fine motor phenotype to brain structural changes and metabolic profiles.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

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Program #/Poster #: 031.22/B18

Topic: A.07. Developmental Disorders

Support: NIH Grant NS R01031348

Title: *Arfgef1* haploinsufficiency in mice reduces neuronal surface GABA_A receptors, increases neuronal lysosome size and upregulates excitatory neurotransmitter receptors

Authors: *J.-J. TEOH¹, N. SUBRAMANIAN^{1,3}, A. KANBER¹, D. WILLIAMS¹, A. AMADOR¹, S. PETRI¹, W. N. FRANKEL^{1,2}

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Abstract: *ARFGEF1* encodes BIG1, an activator of ARF small GTPases, and is involved in intracellular vesicle trafficking. ARFGEFs are candidates for childhood genetic epilepsies. To examine *Arfgef1* haploinsufficiency in mice, we made a 4 nt frameshift mutation in exon 30 (*Arfgef1*^{em3Frk}) in C57BL/6NJ using CRISPR/Cas9. Homozygous *Arfgef1*^{em3Frk/em3Frk} mice die perinatally, similar to previously described knockout mice. *Arfgef1*^{em3Frk/+} heterozygotes survive to adulthood; there is transient weight loss between postnatal day (PND) 14 and PND30, but they catch-up by PND45. Adult heterozygotes show a disruption in the apical lining of the dentate gyrus, but no other gross cell body abnormalities. Although *Arfgef1*^{em3Frk/+} mice do not exhibit obvious spontaneous seizures, they have decreased electroconvulsive threshold compared to wildtype (wt), and are more sensitive to tonic-clonic seizures following injection of 40 mg/kg pentylenetetrazol, the GABA_A receptor antagonist: 75% incidence vs. 12.5% in wt, (p=0.0008) and 571 ± 148 sec vs. 1507 ± 254 sec latency in wt, (p=0.007). In hippocampal neurons culture derived from *Arfgef1*^{em3Frk/+} embryos, at 14 days in vitro (DIV14) there is a reduction of GABA_A receptors on the plasma membrane surface, while total GABA_A receptor is comparable to wt. These neurons also have reduced synapse count. We also noticed that intracellular GABA_A receptors colocalize with lysosomes, and *Arfgef1*^{em3Frk/+} neurons have significantly larger lysosomes compared to wt. Additional immunofluorescence staining showed no striking difference in colocalization of GABA_A receptors with early or recycling endosomes. By using DiI, a lipid based-dye that diffused along plasma membrane, we also determined that hippocampal neurons had longer spine structures at distal dendrites. LC-MS/MS profiling of plasma membrane-enriched brain fractions from PND7 mice showed upregulated expression of presynaptic and postsynaptic membrane proteins as well as excitatory synapse proteins in *Arfgef1*^{em3Frk/+}. Further analysis revealed that proteins functionally annotated as AMPA

glutamate receptor complex, ion channel binding, calcium ion transport and sodium ion export, were among those upregulated. Similar studies from PND21 mice are pending. The decreased neuronal surface GABA_A receptor and accumulation in lysosomes suggests a mechanism whereby impaired neuronal inhibition and excitatory neurotransmitter receptor upregulation leads to seizure susceptibility.

Disclosures: J. Teoh: None. N. Subramanian: None. A. Kanber: None. D. Williams: None. A. Amador: None. S. Petri: None. W.N. Frankel: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.23/B19

Topic: A.07. Developmental Disorders

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Title: Postdoctoral research scientist

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Abstract: *GRIN2A* encodes glutamate ionotropic receptor NMDA type subunit GluN2A. Pathogenic variants in *GRIN2A* are associated with focal epilepsy with or without cognitive or speech-related disability. We identified a rare *de novo* missense variant (resulting in the amino acid substitution S644G) in a child with epilepsy and profound intellectual disability. As part of the JAX Center for Precision Genetics, *Grin2a*^{S644G} mice were generated and males bred with FVB/NJ females to optimize litter size and viability for our studies. Last year we reported on severe spontaneous seizures in *Grin2a*^{S644G} homozygous mutant mice and altered seizure threshold in *Grin2a*^{S644G} heterozygotes. Here, *Grin2a*^{S644G} mutants and wildtype littermates were tested in the Columbia Mouse NeuroBehavior Core for neonatal ultrasonic vocalizations and developmental milestones, open field activity, anxiety-like behavior, fear conditioning, and

Bussey-Saksida touchscreen discrimination learning and reversal. Mutant pups exhibited developmental abnormalities in the first two postnatal weeks. Although body weight was normal, *Grin2a*^{S644G^{-/-}} pups emitted fewer ultrasonic vocalizations, showed impaired righting reflex and sensory-motor reflex. Young adult *Grin2a*^{S644G^{+/-}} mice exhibited reduced anxiety-like behaviors in the elevated plus-maze, hyperactivity, and increased center activity in the open field, indicating reduced behavioral inhibition. To investigate phenotypes that may be relevant to intellectual disability, since that is a feature seen in *GRIN2A* patients, we are pursuing a battery of learning and memory tests. Preliminary results indicate impaired fear conditioning and pairwise discrimination and reversal learning in *Grin2a*^{S644G^{+/-}} mice. In the acquisition phase of the touchscreen test, *Grin2a*^{S644G^{+/-}} mice were slower at acquiring the discrimination task and made more errors, including correction errors. In the reversal phase of the test, wildtype mice had longer response latency than they did in the acquisition phase—an expected reaction to an increase in task difficulty. *Grin2a*^{S644G^{+/-}} mice, however, exhibited an opposed trend of faster responses than in the acquisition phase, indicating impaired executive function. Our data provide strong evidence for the role of *Grin2a*^{S644G} in mouse neonatal physical and sensory/motor development, seizure, behavioral regulation, and cognitive function.

Disclosures: **A. Amador:** None. **M. Yang:** None. **A. Kanber:** None. **E. Ozuruonye:** None. **S. Owens:** None. **H. Olson:** None. **A. Poduri:** None. **D. Goldstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pairnomix, Praxis. **F. Consulting Fees** (e.g., advisory boards); AstraZeneca. **S.F. Traynelis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeurOp Inc. **F. Consulting Fees** (e.g., advisory boards); Sage Therapeutics. **H. Yuan:** None. **M. Boland:** None. **W. Frankel:** None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.24/B20

Topic: A.07. Developmental Disorders

Support: NIH Grant MH112232-02

Title: Developmental psychopathology after maltreatment and disordered attachment within the Strange Situation Test: Insights from an animal model

Authors: ***M. OPENDAK**¹, E. THEISEN¹, D. A. WILSON², R. M. SULLIVAN³

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Abstract: Infants rely on the mother to provide them with the sensory stimulation needed for normal brain development. Altered maternal care, such as maltreatment, initiates a pathway to pathology, much of which remains dormant until later life when mental health is compromised. However, immediate effects can be detected in the maltreated infant by using the Strange Situation Test (SST), which progressively stresses the child to uncover atypical responses to the caregiver (Ainsworth, 1969). Here we adapted this test for use in rat pups to aid in identifying the pups' atypical neurobehavioral features within a maltreatment-associated dyad. Using the Scarcity-Adversity Model of maltreatment induced by low bedding (SAM-LB) for nest building from postnatal days (PN)8-12, we compared SST performance in maltreated rodents (PN13-14) and children; both exhibited behavioral features of disordered attachment in the SST. In pups, recording of cortical oscillations using local field potentials (LFP) showed that the mother had reduced ability to modulate the infant's rhythmic brain activity during SST, compared to pups with no maltreatment experience. Next, we considered the progression of pups' atypical behavior and cortical oscillations by recording LFP in both pup and mother during brief periods of SAM (between PN10-17). Neocortical telemetry LFP electrodes were implanted in PN10 pups and mothers and LFP recorded during 1 hr periods of SAM (maltreatment) or typical rearing in the same animal. Mother-infant interactions were recorded and then scored for behavior and LFP power was decomposed into delta (0-5Hz), theta (5-15Hz), beta (15-35Hz), and gamma (35-80Hz) frequency bands. During the early days of SAM treatment, maltreatment had produced the largest observable effects on both LFP and behavior. With progressing SAM, the dynamic range of LFP induced by mother-pup interactions decreased, with both pup and mother showing impaired LFP responses to specific interactions, such as milk ejection and grooming. These results suggest that when a mother is stressed, she has impaired ability to modulate both her own and pups' neural function. Considering the critical role of brain oscillations in brain functioning and its critical role programming brain development, these maltreatment-related impairments are likely contribution to the pathological developmental pathway induced by maltreatment in early life.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 031.25/B21

Topic: A.07. Developmental Disorders

Support: NIH Grant NS082092
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DOD Grant W81XWH-17-1-0455

Title: Pharmacological blockade of ATX-mediated LPA production prevents posthemorrhagic hydrocephalus in a preclinical lysophosphatidylcholine model

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Abstract: The developing cerebral ventricles contain factors for normal brain growth, signaling, and metabolism. Intracranial bleeding during this critical period can release numerous thrombosis and inflammatory factors and is associated with ventriculomegaly and posthemorrhagic hydrocephalus (PHH) at fetal and neonatal ages. Previously, we demonstrated that fetal brain overexposure to lysophosphatidic acid (LPA) and activation of the cognate LPA receptor LPA₁ induces neonatal hydrocephalus. Here, we extend those findings and report that overexposure to lysophosphatidylcholine (LPC), a blood-derived lipid metabolite converted to LPA via autotaxin (ATX) in cerebrospinal fluid, also induces hydrocephalus, neuroprogenitor cell (NPC) dysfunction, and other ventricle malformations. This is supported by the discovery of altered LPA metabolite and choline levels in CSF from control and PHH patients. The LPC-mediated PHH phenotype appears to depend predominantly on the receptor subtype LPA₁, expressed on NPCs. Prevention of hydrocephalus was achieved using either genetic removal of LPA₁ or inhibition of ATX. This study identifies ATX mechanisms as another target in the growing repertoire for potential pharmacological treatment in neonatal PHH.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.26/B22

Topic: A.07. Developmental Disorders

Support: Z1A-HD001205-24

Title: Parvalbumin-containing inhibitory interneuron migration, morphology, and physiology is altered in Lis1 mutant mice

Authors: *T. G. EKINS^{1,2}, J. A. D'AMOUR¹, C. J. MCBAIN¹

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Abstract: Type I lissencephaly is a neuronal migration disorder caused by Lis1 haploinsufficiency and results in mislamination of brain structures, recurrent seizures, impaired

learning, and motor deficits. In this study, we investigate the impact of Lis1 heterozygous loss on the migration, morphology and physiology of parvalbumin-expressing interneurons (PV-INs) in hippocampal region CA1. To generate mice for this study, we crossed a conditional knock-out line (Lis1^{fl/+}) to different Cre drivers to remove one copy of Lis1 in all cells (Sox2-Cre), exclusively in pyramidal cells (PCs; Emx1-Cre), or selectively in a subset of INs (Nkx2.1-Cre). We observed that by late adolescence, the same number of PV⁺ cells were present in CA1 for all of the Lis1 mutant lines, however, these cells were shifted to more superficial positions. These results indicate that PV-INs reach the hippocampus in normal quantities but are mislocated along the radial axis for all mutant genotypes, suggesting that Lis1 has important cell autonomous and non-autonomous functions in regulating PV-IN radial migration. To investigate how migration deficits impact morphology and intrinsic physiology PV-INs, we recorded and filled RFP⁺ cells from Lis1^{+/-};PV-TdTom mice. While the intrinsic membrane and firing properties of PV-INs are largely unaffected by Lis1 loss, the synaptic physiology is altered; PV-INs in stratum oriens and stratum pyramidale receive a greater frequency of spontaneous excitatory post-synaptic currents. In addition, the axons of Lis1^{+/-} PV-INs are longer and more complex implying that these cells have difficulty finding their correct synaptic partners. To probe further into the connectivity and functionality of PV-INs, we will conduct paired recordings of synaptically coupled PV-INs and PCs. We anticipate that this study will reveal circuit deficits relating to PV-IN function that may underlie the increased propensity for the recurrent seizures observed in Type I lissencephaly.

Disclosures: T.G. Ekins: None. J.A. D'Amour: None. C.J. McBain: None.

Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 031.27/B23

Topic: A.07. Developmental Disorders

Support: NINDS NS091170
U54 NS100064

Title: Decanoic acid can lead to suppression of spasms in the multiple hit rat model of infantile spasms due to structural lesion

Authors: *A.-M. KATSAROU¹, W. B. MOWREY², Q. LI¹, W. LIU¹, S. L. MOSHÉ³, R. S. B. WILLIAMS⁵, A. S. GALANOPOULOU⁴

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Abstract: Background: West syndrome is a severe infantile epileptic encephalopathy that manifests with infantile spasms (IS) and has poor neurodevelopmental and epilepsy deficits. The classical ketogenic diet has been tried as an adjunctive treatment for IS. Fats provided in the medium chain triglyceride (MCT) ketogenic diet, including decanoic acid (DEC), have been proposed to mediate some of the therapeutic effects of the diet, but have not been investigated for the treatment of IS. **Objective:** To test if DEC, given after spasms onset, can suppress spasms in the multiple-hit rat model of IS due to structural lesion, on its own and without additional ketogenic diet restrictions. **Methods:** Postnatal day (PN) 3 Sprague-Dawley male rats received right intracerebral injections of Doxorubicin and Lipopolysaccharide followed by intraperitoneal injection of systemic p-chlorophenylalanine (PCPA) on PN5 (DLP rats). Body weights, surface righting time (SRT), open field activity (OFA) and negative geotaxis (NG) were scored between PN3-5. Using a randomized, blinded vehicle-controlled, dose-response study design, DEC (0.1, 0.25, 0.5, or 5mM) or vehicle was given i.p. on PN4 PM, as a single injection in each group (VEH: n=14, 0.1mM DEC: n =13, 0.25 mM DEC: n=10, 0.5mM DEC: n=9, 5mM DEC: n=7). Two hours video monitoring sessions were done on PN4AM, PN5AM and PN5PM and a longer session consisting of 1 pre- and 5 post-injection hours was done on PN4PM, when the drug was given. On PN5, pups were euthanized with pentobarbital and brains were frozen for histology. Statistics on log-transformed data of raw or normalized over the baseline frequencies of spasms used a linear mixed model accounting for repeated measures. **Results:** Rats treated with 5mM DEC had lower raw and normalized spasms rates compared to VEH at the 2nd and 4th hour after drug administration on PN4 (P<0.05). No differences in the weights, weight gain rates, milestones till PN5 or no drug-related mortality were observed. **Discussion:** The highest dose of decanoic acid reduced spasms during the 2nd and 4th post-injection hour and was well tolerated in pups, suggesting that MCTs may have an effect on spasms without implementing additional ketogenic diet restrictions.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 031.28/B24

Topic: A.07. Developmental Disorders

Support: ANR/FCT (FOXNET)
Bial Foundation (192/12)
ERC (COG 617142)

Title: Dissecting the contributions of Foxp1 and Foxp2 to motor behavior

Authors: *L. G. STOICA GHITA¹, C. A. FRENCH², S. F. GOMES², M. GROSZER¹, R. M. COSTA^{3,2}

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Abstract: Developmental brain dysfunction can result in a spectrum of impairments which affect a broad range of behavioral domains including higher cognition, social interaction, verbal and non-verbal communication and motor function. However, little is known about how genetic interactions converging on common downstream cellular and molecular networks result in aberrant function in defined circuits and ultimately cause specific endophenotypes.

FOXP1 and FOXP2 are members of the highly evolutionary conserved FOXP family of transcription factors. *FOXP1* heterozygous mutations were identified in patients with autism, gross motor delay and intellectual disability whereas disruptions in one copy of the *FOXP2* gene cause language impairments and verbal dyspraxia, difficulty in generating fine orofacial movements required to produce normal speech. Both proteins function as homo or heterodimers to regulate transcription of common downstream targets, suggesting that they might share common underlying molecular and circuit mechanisms. Given that a) *Foxp1* and *Foxp2* have overlapping expression in the striatum, a brain region critical for acquisition and performance of learned actions, b) *Foxp2* has been implicated in motor-skill learning in mice and humans and c) mice with *Foxp1* or *Foxp2* mutations exhibit abnormal plasticity of striatal medium spiny neurons, we set out to investigate how genetic dosage differences in these proteins can influence specific aspects of motor behavior.

We intercrossed *Foxp1*^{+/-} mice (*Foxp1* het) and *Foxp2*^{+/-} mice (*Foxp2* het) to generate double heterozygote animals (dHet) and wild-type (wt) controls. All genotypes resulting from this cross were born at Mendelian ratios, displayed normal locomotor activity levels, as well as no overt anxiety phenotype in the open field. First, we used pharmacology to study the locomotor stimulating effects of cocaine. Wt and *Foxp1* het animals displayed robust hyperlocomotion, while *Foxp2* het mice had an attenuated locomotor response. Surprisingly, dHet animals showed a partial rescue phenotype. These results suggest a compensatory effect of *Foxp1* in a *Foxp2* background when dopamine signaling is pharmacologically activated. We also examined motor-skill learning in this cohort of animals using the accelerating rotarod. No deficits were observed in *Foxp1* het mice. Contrary to the cocaine experiments, the dHet was more severe than the *Foxp2* het phenotype suggesting that in some cases the two genes function cooperatively. We are currently investigating how natural patterns of motor behavior are affected and are also trying to identify relevant underlying circuits.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

Location: SDCC Halls B-H

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Topic: A.07. Developmental Disorders

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Title: Deficiency of protocadherin 1 cell adhesion molecule enhances social behavior in mice

Authors: *S. HIRANO¹, T. FURUSE², S. HAYASHIZAKI¹, K. OKANO-IMAI¹, S. WAKANA^{2,3}

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Abstract: Protocadherins constitute the largest family of cadherin superfamily genes. Protocadherin 1 (Pcdh1) is expressed in various parts of the developing nervous system including hippocampus, cerebral cortex, and amygdala. To determine the roles of Pcdh1 in the nervous system, we generated a Pcdh1 knock-out (Pcdh1-KO) mouse line by gene targeting (established by RIKEN CLST LARGE), and analyzed its histology and behavior. Pcdh1-KO mice look healthy with normal body weight although activity of a few enzymes of blood was slightly changed. The gross morphology of the brain and major neural tracts of Pcdh1-KO mice, visualized with the anti-neurofilament antibody, was normal. Then, we examined roles of Pcdh1 in neural functions. We tested the behavior of Pcdh1-KO mice systematically using the RIKEN modified SHIRPA method of the Japan mouse clinic (RIKEN BRC), which includes light/dark transition test, open-field, Crawley's social interaction test, home-cage activity test, Y-maze test, fear conditioning test, and pre-pulse inhibition test (http://ja.brc.riken.jp/lab/jmc/mouse_clinic/en/business/pipeline.html). In the light/dark transition test, Pcdh1-KO mice were normal. In the open-field test, Pcdh1-KO mice had a tendency to travel longer distance in the peripheral zone. In the Crawley's social interaction test, Pcdh1-KO mice showed a tendency to spend more time near an unfamiliar stimulus mice. In the home cage activity test, activity of the Pcdh1-KO mice was reduced. In the Y-maze test, Pcdh1-KO mice travelled a longer distance. In the fear conditioning test, learning of the Pcdh1-KO was normal.

In the pre-pulse inhibition test, *Pcdh1*-KO mice showed normal inhibition although they showed lower startling response at a certain point. These results suggested that *Pcdh1*-KO mice showed higher activity in unfamiliar environments, but their activity was lower in the home cage. In addition, sociability of the *Pcdh1*-KO mice was enhanced compared to that of the wild-type mice. Taken together, we suggest that *Pcdh1* may be involved in neural functions underlying emotional and social behavior.

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Poster

031. Developmental Disorders: Animal Models of Neurodevelopmental Disease I

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Program #/Poster #: 031.30/B26

Topic: A.07. Developmental Disorders

Support: ZIA MH000889
FRAXA Postdoctoral Fellowship

Title: Characterization of the behavioral phenotype of a tuberous sclerosis complex mouse model

Authors: *A. LEMONS, R. M. SARE, C. FIGUEROA, C. B. SMITH
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Abstract: Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic disorder that affects approximately 1/6000 people. TSC is caused by a mutation in either *TSC1* or *TSC2* which code for the proteins hamartin and tuberin, respectively. These proteins form a complex that inhibits mammalian target of rapamycin complex 1 (mTORC1). Mutations in either *TSC1* or *TSC2* lead to overactivation of the mTORC1 pathway and consequently dysregulated cell growth and proliferation. In addition to benign tumors that form systemically, patients with TSC display a range of behavioral manifestations including intellectual disability, autism spectrum disorders, attention deficit hyperactivity disorder, anxiety, mood disorders, and sleep problems. Patients with mutations in *TSC2* tend to display a more severe neurological phenotype. To better understand the relationship between a mutation in *Tsc2* and behavioral deficits, male and female wild type (WT) and *Tsc2*^{+/-} mice (n=14-40) were tested on a battery of behavioral tests. Testing began at about 70 days of age. Results were analyzed by two- or three-way ANOVA. As a measure of anxiety in the open field test, we compared the ratio of center to total distance traveled. Analysis of these data indicated a statistically significant epoch x sex x genotype interaction (p=0.014) indicating that male *Tsc2*^{+/-} mice habituate to the novel environment more quickly suggesting reduced anxiety compared to other groups. On another test of anxiety, zero

maze, we found a main effect of genotype ($p=0.067$), suggesting that $Tsc2^{+/-}$ mice, regardless of sex, show less anxiety compared to WT. The sociability test revealed a sex x chamber interaction ($p=0.017$) indicating that male mice, regardless of genotype, spend more time with a stranger mouse compared to a novel object; female mice (both WT and $Tsc2^{+/-}$) did not show this preference for sociability. In the social novelty test the genotype x sex x chamber interaction approached significance ($p=0.07$). Male WT, but not male $Tsc2^{+/-}$ mice, tended to show a preference for the novel mouse ($p=0.086$). Female $Tsc2^{+/-}$ mice showed a similar preference for social novelty ($p=0.019$). In contrast, WT female mice did not show this preference. These data indicate that male, but not female, $Tsc2^{+/-}$ mice have social behavior deficits that may signify autistic-like behavior. Taken together, these behavioral data suggest that the $Tsc2^{+/-}$ mouse model recapitulates some, but not all, of the possible behavioral deficits reported in human TSC patients. Developing a more complete understanding of the behavioral phenotype of $Tsc2^{+/-}$ mice allows us to better test the ability of pharmacological treatments to improve behavioral deficits.

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Poster

032. Developmental Disorders: Animal Models of Autism

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Program #/Poster #: 032.01/B27

Topic: A.07. Developmental Disorders

Support: PAPIIT-UNAM grants IN201913
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Title: Cerebellar GABA ρ 3 expression is reduced in the valproic acid model of autism

Authors: *B. SORIA-ORTIZ, D. VARMAN, A. MARTÍNEZ-TORRES, D. REYES-HARO
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Abstract: Autism spectrum disorders (ASD) are a group of developmental disabilities characterized by social interaction deficits, inadequacy of communication, stereotyped and repetitive behaviors. Imbalance of excitatory/inhibitory activity associated with GABAergic circuitry have been linked with ASD. Postmortem studies in the cerebellum from diagnosed ASD individuals showed a reduced density of Purkinje cells (PCs) and abnormal expression of GABA-A subunits. Among GABA-A subunits, GABA ρ 3 is known to be expressed in early postnatal development of the murine cerebellum. GABA ρ 3, like other GABA ρ subunits, forms homomeric receptors with high affinity for the agonist (GABA EC $_{50}$ about 3 μ M) and desensitize very little upon activation. These properties make them potentially relevant to detect developmental signaling cues, such as those triggered by GABA; particularly because ASD is a neurodevelopmental disorder. Thus, we tested if the expression of GABA ρ 3 was modified by

prenatal exposure to valproic acid (VPA), a well-known model of autism. Pregnant mice were injected intraperitoneally at embryonic day 12.5 with either 500 mg/kg VPA or 0.9% saline solution (CTL). Anatomical and behavioral analyses were performed in male pups since ASD incidence is higher in males (4:1). First, brains of VPA-treated mice were heavier than controls (0.216 ± 0.012 g, n = 18 for CTL and 0.256 ± 0.009 g, n = 17 for VPA, $p < 0.05$), at postnatal day 8 (P8); whereas at P18 brain weight of VPA-treated mice was reduced with respect to controls (0.397 ± 0.008 g, n = 6 for CTL and 0.359 ± 0.007 g, n = 17 for VPA, $p < 0.01$). Second, the latency to reach the nest was used to analyze social deficits. The latency was increased in VPA-treated mice compared to controls (56.7 ± 4.1 s, n = 15 for CTL and 153 ± 9.8 s, n = 15 for VPA, $p < 0.0001$). Western blot from cerebella of VPA-mice revealed reduced expression of PCs-marker calbindin and GABA ρ 3 (-22% and -23%, respectively; n = 6 $p < 0.0001$). Moreover, immunofluorescence showed reduced density of Purkinje cells at P8 in lobules VII (39 ± 2 cells/mm, n = 8 for CTL and 31 ± 2 cells/mm, n = 8 for VPA, $p < 0.001$) and X (55.14 ± 2.5 cells/mm, n = 6 for CTL and 33.80 ± 1.7 cells/mm, n = 6 for VPA, $p < 0.01$). Finally, EGCs expressing GABA ρ 3 were reduced by VPA (22 ± 3 cells/mm for CTL and 15 ± 1 cells/mm for VPA, n = 3, $p < 0.05$). We conclude that GABA ρ 3 expression is reduced by prenatal exposure to VPA in Purkinje and ependymal cell layers. Thus, GABA ρ 3 may be a relevant marker for ASD etiology.

Disclosures: **B. Soria-Ortiz:** None. **D. Varman:** None. **A. Martínez-Torres:** None. **D. Reyes-Haro:** None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.02/B28

Topic: A.07. Developmental Disorders

Title: Comparison of excitatory synaptic transmission in the striatum and nucleus accumbens in four mouse models of autism-spectrum disorder

Authors: **K. KRETSCHMANNOVA**, J. SANCHEZ-PADILLA, S. GELMAN, J. PALMA, H. FERNANDES, G. TOMBAUGH, M. KWAN, J. BELTRAN, A. GHAVAMI, *E. LEAHY
Psychogenics, Paramus, NJ

Abstract: Autism-spectrum disorder (ASD) is characterized by profound social deficits including difficulties with communication and social interaction, and by the presence of restricted and repetitive behaviors and interests (RRBI). A growing body of evidence points to the involvement of basal ganglia in ASD-related pathophysiology with striatal dysfunction underlying RRBI. Here we compared the excitatory synaptic transmission in the striatum and nucleus accumbens in four genetic models of ASD: Shank3 KO (Feng), Cntnap2 KO (Pele),

Fmr1 KO and Mecp2 KO (Bird). We used extracellular field potential recordings and whole-cell patch clamp recordings from medium spiny neurons to assess corticostriatal synaptic transmission in dorsal striatum and extracellular field potential recordings to examine intra-nucleus accumbens synaptic transmission in these mouse models. In an attempt to correlate potential impairment in synaptic transmission with gene changes, we also evaluated mRNA expression levels of PSD95, synaptophysin, AMPA and NMDA receptor subunits in the striatum and BDNF isoforms in the cortex. Examination of synaptically-driven population spikes revealed functional deficits in dorsal striatum and nucleus accumbens of Shank3 KO mice. Both, evoked AMPA- and NMDA-receptor mediated currents from medium spiny neurons in dorsal striatum were reduced in this ASD mouse model. These findings were paralleled by the changes in the expression of synaptic proteins. We found significantly reduced levels of transcripts for PSD95, synaptophysin, GluA1, GluA2, GluN2A and GluN2B in the striatum and BDNF isoforms I, IV, VI and IX in the cortex. Despite the importance of the striatum for the control of RRBI and the role of nucleus accumbens in social reward, other examined ASD mouse models did not show any deficits in either corticostriatal or intra-nucleus accumbens synaptic transmission. Further analysis is needed to understand specific changes in basal ganglia circuits and sub-circuits and how their dysfunction contributes to ASD symptomatology.

Disclosures: **K. Kretschmannova:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **J. Sanchez-Padilla:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **S. Gelman:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **J. Palma:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **H. Fernandes:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **G. Tombaugh:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **M. Kwan:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **J. Beltran:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **A. Ghavami:** A. Employment/Salary (full or part-time);; PsychoGenics Inc. **E. Leahy:** A. Employment/Salary (full or part-time);; PsychoGenics Inc..

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.03/B29

Topic: A.07. Developmental Disorders

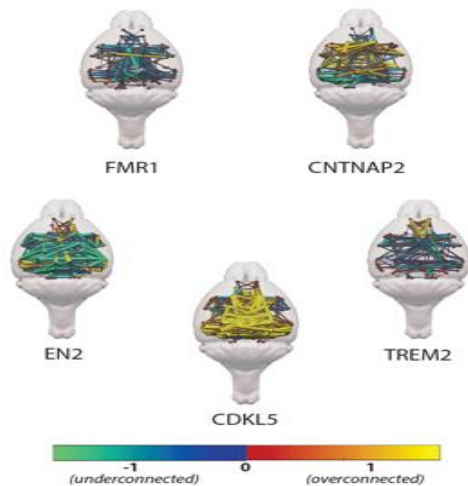
Support: ETH Career Seed Grant No. SEED-42 16-1
SNSF AMBIZIONE PZ00P3_173984 / 1
SFARI #400101

Title: The autism mouse brain connectome project

Authors: *V. ZERBI¹, M. MARKICEVIC¹, M. PAGANI², M. RUDIN³, M. MATTEOLI⁴, M. FAGIOLINI⁵, Y. BOZZI⁶, G. PROVENZANO⁷, A. BANERJEE⁸, J. ELLEGOOD⁹, J. P. LERCH¹⁰, A. GOZZI², N. WENDEROTH¹

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Abstract: Autism Spectrum Disorders (ASD) are highly heterogeneous conditions with respect to both etiology and symptoms, which presents a substantial challenge to diagnosis and treatment. One emerging hypothesis is that within the autism spectrum there are common modes of dysfunctional pathways at the brain network level. Here we introduce the **Autism Mouse Brain Connectome** initiative. This study, born in conjunction between ETH Zürich and the Istituto Italiano di Tecnologia (IIT), uses MRI-based brain functional connectomic measurements in combination with mouse mutants relevant for ASD. The aim is to identify generalizable connective deficits across Autism-associated mutations, and use it to gain insight into the genetic heterogeneity of ASD. Resting-state fMRI datasets are acquired in both centers on 7T Bruker scanners, using well-established protocols to sedate and monitor mice. Data are cleaned from artifacts and analyzed following guidelines from the Human Connectome Project. Deviations from wildtype littermates' connectivity in each mouse model define gene-specific pathological connectomic profiles. On February 2018, rs-fMRI scans of eleven mouse models have been successfully acquired at ETH (*Fmr1*^{-y}, *CNTNAP2*^{-/-}, *EN2*^{-/-}, *TREM2*^{-/-}, *CDKL5*^{-/-}, *MeCP2*^{-x}) and IIT (*BTBR*, *SynII*^{-/-}, *Shank3b*^{-/-}, *16p11.2*^{-/-}, *CHD8*^{-/-}). By mid-2018 we plan to reach our target of 20 models scanned. Preliminary results indicate the presence of network-specific abnormal connectivity in all analyzed models. Computational approaches leading to a unified clustering of the functional changes observed in the models will be employed to group mutations based on their effect on macroscale functional coupling. The identification of convergent pathways at the network level will define endophenotypes within the autism spectrum that could benefit from targeted circuit-specific treatments.



Disclosures: V. Zerbi: None. M. Markicevic: None. M. Pagani: None. M. Rudin: None. M. Matteoli: None. M. Fagiolini: None. Y. Bozzi: None. G. Provenzano: None. A. Banerjee: None. J. Ellegood: None. J.P. Lerch: None. A. Gozzi: None. N. Wenderoth: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.04/B30

Topic: A.07. Developmental Disorders

Title: Cortical network graphs and dynamic functional connectivity in a mouse model of autism spectrum disorder

Authors: *C. J. MACDOWELL, T. J. BUSCHMAN
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Abstract: Clinical studies routinely report aberrant functional connectivity across cortical regions in Autism Spectrum Disorder (ASD). However, the patterns of these findings are highly heterogeneous and inconsistent between studies. This is likely due to the complex etiologies and behavioral phenotypes of ASD. Thus, a detailed understanding of aberrant connectivity patterns, their underlying neurobiological mechanisms, and relationship to behavioral pathologies would benefit considerably by large-scale functional connectivity analyses in well-controlled animal models of different putative ASD genetic and epigenetic etiologies. Here we used a combination of functional connectivity analyses and graph theoretical approaches to build a detailed map of cortical connectivity patterns in an *in utero* Valproic acid exposure mouse model of ASD and saline-exposed controls. We investigated cortical connectivity patterns at a high spatial and temporal resolution by using through-skull, wide field calcium imaging to record activity of

GCAMP6f-expressing pyramidal cells across the entire dorsal cortex of awake, head-fixed mice. We imaged resting-state activity and evoked responses to auditory, tactile, and visual stimuli. We then used seed-based correlation analyses to build graphs of functional networks both across entire 12-minute resting-state recording sessions (e.g. static functional connectivity) and within 30-second sliding-window epochs (e.g. dynamic functional connectivity). Furthermore, we investigated whether graph features of stimulus-evoked networks differed between groups. Finally, to better elucidate the relationships of these cortical network graphs to behavioral pathologies, we correlated individual animals' graph characteristics to the results of an extensive battery of neurodevelopmental and behavioral tests performed from birth through young adulthood in each animal. This work lays the groundwork for understanding the neurobiological underpinnings of ASD-related aberrant cortical connectivity patterns.

Disclosures: C.J. Macdowell: None. T.J. Buschman: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.05/B31

Topic: A.07. Developmental Disorders

Support: Ministry of Health & Welfare, Republic of Korea, HI15C1834

Title: Disruption of the dorsal striatum function promotes autistic-like behaviors

Authors: *Y. LEE¹, H. KWON¹, P.-L. HAN^{1,2,3}

¹Dept. of Brain and Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of; ²Brain Dis. Res. Inst., ³Dept. of Chem. and Nano Sci., Ewha Womans Univ., Seoul, Korea, Republic of

Abstract: Autism spectrum disorder (ASD) is a group of psychiatric disorders characterized by the two core domains of behavioral symptoms, namely social communication deficits and restricted repetitive behaviors. The fundamental question of whether the ASD core symptoms are produced by dysfunction of neural network(s) distributed widely in the brain or in specific brain region(s) is not clearly answered. Recently, we reported that mice lacking adenylyl cyclase 5 (AC5 KO mice) displayed autistic-like behaviors including sociability deficits and repetitive behaviors. AC5 is preferentially expressed in the dorsal striatum that receives extensive synaptic inputs from glutamatergic and dopaminergic neurons. Optogenetic stimulation of the cortico-striatal glutamatergic input induced sociability deficits. Mice lacking dopamine D2 receptor (D2 KO mice) also showed autistic-like behaviors including sociability deficits and repetitive behaviors. Moreover, mice with increased dopamine functions in the dorsal striatum through the suppression of dopamine transporter expression in substantia nigra neurons or by the optogenetic stimulation of the nigro-striatal circuitry exhibited sociability deficits and repetitive behaviors,

while these behavioral changes were blocked by a dopamine D1 receptor antagonist. Local knockdown of AC5, D2, or mGluR3 in the dorsal striatum of wildtype mice produced autistic-like behaviors. Specific knockdown of MeCP2 or Tsc1, which are well-known ASD-related genes and are not directly related to D2 or AC5 function, in the dorsal striatum of wildtype mice also induced sociability deficits and increased grooming behaviors. Together, our results suggest that the dorsal striatum is the critical brain region whose dysfunction produces ASD core symptoms, and raise the possibility that ASD core symptoms may be controlled by rebalancing the dorsal striatum function.

Disclosures: Y. Lee: None. H. Kwon: None. P. Han: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

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Program #/Poster #: 032.06/B32

Topic: A.07. Developmental Disorders

Support: Cuerpo Académico de Neuroquímica UV-CA- 304
Cuerpo Académico de Neurociencias UV-CA- 28
Registro Becario CONACyT: 577042

Title: Fos expression profile in suprachiasmatic nucleus in a postnatal valproate rat model of autism at different ages in a 24-hour cycle

Authors: *G. J. SÁNCHEZ¹, B. A. LARA¹, M. HERNANDEZ², G. E. ARANDA-ABREU², L. I. GARCIA², J. MANZO², R. TOLEDO-CARDENAS²

¹Doctorado en Investigaciones Cerebrales, Ctr. de Investigaciones Cerebrales, Xalapa, Mexico;

²Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico

Abstract: Autism spectrum disorder (ASD) is diagnosed according to three main features: social deficits, communication impairments and stereotyped behaviors. However, hormonal rhythms alterations and sleep-wake cycle disorders are present in children with autism. Valproic acid exposure (VPA) during critical periods of development mimics several characteristics of autism. Currently, the rat has been proposed as a valid animal model for the study of ASD by using VPA as teratogen. In this case, VPA is applied both in prenatal (E) or postnatal (P) ages, to study how is the development of the nervous system under this insult. Such is the case of the suprachiasmatic nucleus (SCN), main pacemaker of biological rhythms. In rodents, SCN is still immature in the first two weeks after birth and it is unclear how this structure is affected in individuals with ASD. The objective of the present study was to evaluate the expression of the c-Fos protein as a marker of neuronal activity in the SCN in neonatal rats treated with VPA in a 24h-period. Male and female Wistar rats were used to evaluate the number of immunoreactive

(IR) cells of the SCN. The animals were divided by age into two groups, P15 and P25. Then, each group was divided by treatment: VPA group (150 mg/kg), injected from P06 to P12, and saline group (0.9%) as controls in the same ages. Rats were kept under a 12:12 LD cycle. To investigate the rhythmicity of c-Fos expression in the SCN, sampling was taken at precise time points: ZT01, ZT07, ZT13 and ZT19 (n=6). Results show both VPA and control groups had c-Fos expression induced by light in ZT01 and ZT09, with a tendency to decrease the number of IR cells in ZT13 and ZT19 (dark phase) for both ages. Regarding age differences, the VPA-P15 group showed an increase in the number of c-Fos-IR cells at all ZT compared to the controls, showing ZT07 the highest number of c-Fos-IR cells. In P25, both the VPA animals and the controls presented a similar c-Fos-IR for all ZT with no differences at any point. According to the results, it is suggested that the SCN in rats VPA-P15 has an intense stabilization process. However, it is important to note that the influence of the mother's circadian clock at this age can help the system to stabilize as apparently happens in the VPA-P25 rats. Therefore, we suggest that the neuronal activation of animals VPA-P15, may not necessarily be functional, since it is not clear whether the c-Fos-IR cells execute coordinated actions to synchronize the SCN. Through the rat VPA model, it is important to conduct behavioral and neuronal activity studies of the SCN at all stages of development. This study provides data to understand autism from the regulation of biological rhythms.

Disclosures: G.J. Sánchez: None. B.A. Lara: None. M. Hernandez: None. G.E. Aranda-Abreu: None. L.I. Garcia: None. J. Manzo: None. R. Toledo-Cardenas: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.07/C1

Topic: A.07. Developmental Disorders

Support: Hussman Institute grant HIAS18001

Title: Inhibitory synaptic transmission by parvalbumin-positive interneurons is perturbed in *Cntnap2*-KO autism model mice

Authors: *M. BRIDI¹, S. HUANG²

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Abstract: Genetic studies in humans provide strong evidence that changes in synaptic function and neuronal connectivity are common factors in autism pathophysiology. Human and animal studies both suggest that such dysfunction leads to excitatory/inhibitory (E/I) imbalance in the form of reduced inhibition and/or over-excitation, and that both pre- and post-synaptic changes may impact neuronal inhibition. *Cntnap2* knockout (KO) mice are an established model of

Autism Spectrum Disorder (ASD) that exhibit autism-like phenotypes including hyperactivity, stereotyped behavior, reduced interneuron numbers, seizure activity, and alterations in synaptic spines. Previously we demonstrated that *Cntnap2* deletion leads to a developmentally-dependent reduction in phasic inhibitory currents and decreased spontaneous IPSC frequency in layer 2/3 pyramidal cells in primary visual cortex, V1. Here we sought to investigate the effects of *Cntnap2* KO on the function of parvalbumin-positive interneurons (PV-INs) and inhibitory neurotransmission. E/I ratio in V1 pyramidal cells was tested by electrical stimulation of feed-forward L4 to L2/3 synapses. We found that in KO mice the E/I ratio was higher than in wildtype (WT) mice, indicating increased excitatory input and/or reduced inhibitory input onto V1 principal neurons. We generated a line of *Cntnap2*-KO \times PV-Cre mice to facilitate the identification and stimulation of PV-INs. We used whole-cell recording to measure IPSCs in L2/3 pyramidal neurons evoked by trains of optogenetic stimulation of ChR2-expressing PV-INs in visual cortical slices. At high frequencies/short interstimulus intervals, paired-pulse depression was higher in KOs than in WTs, indicating higher initial probability of evoked release from PV-INs. We also recorded from fluorescently-labeled PV-INs in V1 to assay the basic properties of this cell type, and found that resting membrane potential and action potential threshold were slightly but significantly higher in KO mice. We found no effect of genotype on amplitude, frequency, or kinetics of miniature EPSCs. These data indicate that in visual sensory cortex of *Cntnap2*-KO mice cell-autonomous PV-IN function is largely normal, but that inhibitory synaptic connections are altered in a manner that impairs GABAergic inhibition and postsynaptic inhibitory currents. Our findings further support the notion that disruptions in inhibitory circuitry could underlie autism-like behaviors, and suggest that future studies should investigate the mechanisms of reduced inhibition and the effects of diminished PV⁺ interneuron function in sensory processing.

Disclosures: M. Bridi: None. S. Huang: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.08/C2

Topic: A.07. Developmental Disorders

Support: Universidad Nacional, Hermes 41667

Title: Morphological, behavioral and molecular alterations in the rodent model of autistic spectrum disorder

Authors: J. MORENO-AVENDAÑO¹, F. CÁRDENAS², *Z. DUENAS³

¹Medicina, Univ. Nacional de Colombia, Bogotá D.C., Colombia; ²Psicología, Univ. de los Andes, Bogotá D.C., Colombia; ³Univ. Nacional De Colombia, Bogota DC, Colombia

Abstract: Autism spectrum disorder ASD, is a neurodevelopmental disorder characterized by three main behavioral symptoms including social deficits, impaired communication, and stereotyped and repetitive behaviors. Valproic acid, VPA, is a powerful teratogen of commonly prescribed anticonvulsants, causing birth defects in humans, including ASD, if exposure occurs during the first trimester of embryogenesis. The causal relationship between prenatal exposure to VPA and the development of ASD symptoms support a large number of animal studies. The VPA rat model is an environmentally triggered model, useful to understand the genetic and molecular levels of the ASD pathology. Current theories of ASD relate symptom development to factors that alter learning and memory, but underlying molecular and synaptic alterations remain unknown. *N*-methyl-D-aspartate receptor, NMDAR, dependent long term changes in synaptic efficacy in the mammalian CNS are thought to represent underlying cellular mechanisms for some forms of learning. Previous work has shown that neuron physiology in VPA-exposed animals is marked by impairment in intrinsic neuronal excitability and increase in NMDA synaptic currents, but the molecular mechanisms that explain this dysfunction are not clear. In this study, we investigated whether anomalies in postnatal development are related with atypical expression of a specific subunit of NMDAR in the prefrontal cortex, hippocampus and cerebellum of prenatally VPA-exposed animals. Our results regarding to behavioral validation of the animal model showed a high rate of fetal reabsorption in treated females, while the offspring showed significant morphological changes and behavioral alterations. There was an increase in the number of births with physical malformations, defects in the formation of the fingers, length and shape of the tail and sporadic cases of chromodacriorrhea, while the behavioral tests: sociability test and grooming, showed alterations in sociability and repetitiveness, typical behaviors of the human autistic phenotype. In addition, our molecular results suggest functional impairments in the structural conformation of NMDAR may be one of the underlying mechanisms leading to the abnormal behavior in VPA rat model, and possibly in human ASD.

Disclosures: J. Moreno-Avedaño: None. F. Cárdenas: None. Z. Duenas: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.09/C3

Topic: A.07. Developmental Disorders

Support: NLM

NICHD funded IDDRC 054 (U54HD079125)

Title: *In vivo* magnetic resonance spectroscopy detects alterations of brain metabolites in a rat model of maternal autoantibody-related autism

Authors: *M. R. BRUCE¹, R. MADDOCK², D. ROWLAND², M. D. BAUMAN², J. VAN DE WATER²

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Abstract: Dysregulation of the maternal immune system has been increasingly implicated in the causality of various neurodevelopmental disorders in offspring, particularly when considering Autism Spectrum Disorders (ASDs). A number of recent studies have focused on the relationship between the presence of specific autoantibodies found in the maternal circulation and the diagnosis of ASD in children. We previously characterized a set of antigenic epitopes on proteins, known to be important for neurodevelopment, which serve as targets for these maternally-derived autoantibodies. Furthermore, collaborative work has identified that these antibodies are able to bind radial glial cells in the developing cortex of embryonic rodents and influence radial glial migration and proliferation as well as cortical development and connectivity. To examine the potential neurochemical imbalance that may underlie differential aspects of neurodevelopment in a rat model of maternal autoantibody-related autism (MAR-ASD), we first immunized rat dams with LDHA, LDHB, CRMP1 and STIP1 MAR-ASD specific peptides to generate autoantibodies in dams prior to breeding. Once offspring were born, we performed *In vivo* longitudinal magnetic resonance spectroscopy (MRS) to evaluate levels of metabolites in the rat brain between MAR autoantibody exposed (n= 8) and control animals (n= 8) at pre- and post-pubertal time points (postnatal days 30 and 70, respectively). To date, we have found that the presence of MAR autoantibodies during gestation results in altered GABA levels in the brain, as well as other molecules important in regulating cellular metabolism. These experiments suggest that exposure to specific maternal autoantibodies may alter gross GABAergic transmission in a rat model of MAR ASD.

Disclosures: M.R. Bruce: None. R. Maddock: None. D. Rowland: None. M.D. Bauman: None. J. Van de Water: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

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Program #/Poster #: 032.10/C4

Topic: A.07. Developmental Disorders

Support: CONACyT grant 572788
CONACyT grant 252808

Title: Behavioral and morphological changes in the rat limbic system in an animal model of autism, exposure to propionic acid in the prenatal age

Authors: *S. I. GONZALEZ CANO¹, M. E. BRINGAS¹, I. CAMACHO-ABREGO¹, G. FLORES¹, M. ATZORI², D. MACFABE³

¹Inst. de Fisiología BUAP, Puebla, Mexico; ²Univ. Autónoma de San Luis Potosí, San Luis Potosí, Mexico; ³KileePatchell-Evans Autism Res. Group, Alberta Children's Hosp. Res. Inst., Calgary, AB, Canada

Abstract: Autistic Spectrum Disorder (ASD) is a disorder of neurological development of multifactorial etiology. It is characterized by deficiencies in verbal and social communication, altered social behavior and poor sensory functioning, in addition to stereotype and repetitive behavior. Several investigations have focused on the role played by the gut microbiota on the etiology of autism. There is strong evidence that alterations in the microbiota-gut-brain axis influence the pathogenesis of autistic spectrum disorder. Several authors report abnormal levels of bacterial colonies e.g, *Clostridia*, *Bacteroidetes* and *Desulfovibrio* subtypes, in the gastrointestinal tract of autistic children. The metabolic products of these microorganisms include short chain fatty acids (SCFA) such as acetate, butyrate and propionic acid (PPA). The SCFA at physiological level is essential for intestinal and immune function; however, high levels alter the immune function and/or exacerbate behaviors associated with ASD. The SCFA, propionic acid (PPA), is a metabolic product of enteric bacteria and a potential environmental factor in the development of ASD. Currently, prenatal exposure to propionic acid has been proposed as a neurodevelopmental model of cognitive and behavioral abnormalities similar to ASD in the rat (MacFabe 2015, *MicrobEcol Health Dis*, 26, 28177). For this reason, this work consisted in evaluating the effect of prenatal administration of PPA (500 mg/Kg, SC, DG12 to DG16) in male rats of the Sprague Dawley strain during three different stages of its development; childhood (21 DP), prepubertal (35 DP) and postpubertal (70 DP). In particular, it was examined: 1) Neuronal morphology (Golgi-Cox method) (Bringas et al., 2013, *Neuroscience*, 241, 170). 2) Learning and memory (test of novel objects recognition (NOR) for its acronym in English Novel Object Recognition) and 3) Social behavior (social interaction test). The analysis was made in the Prefrontal Cortex (CFP) and Dorsal Hippocampus (HD), two cerebral regions of the limbic system involved in the study of ASD. The data obtained show deterioration in learning processes and memory during early stages of the animal's life, as well as alterations in social behavior. Additionally, alterations in the neuronal cytoarchitecture of CA3 and GD during the stages of childhood and prepubertal were observed. These results suggest a direct participation of PPA in the generation of the symptoms related to ASD.

Disclosures: S.I. Gonzalez Cano: None. M.E. Bringas: None. I. Camacho-Abrego: None. G. Flores: None. M. Atzori: None. D. MacFabe: None.

Poster

032. Developmental Disorders: Animal Models of Autism

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Program #/Poster #: 032.11/C5

Topic: A.07. Developmental Disorders

Support: NSFC 91649115

NSFC 31701297

NSFC 31490592

MH098114

Ministry of Science and Technology (2014CB942803)

Title: SHANK3 deficient monkeys reveal the critical function of SHANK3 and autism-like symptoms

Authors: ***T. ZHUCHI**¹, Y. SEN¹, Z. HUI², L. BANG¹, G. XIANGYU¹, L. SHIHUA³, Z. YONGQING², L. XIAOJIANG^{1,3}

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Abstract: Mutations in the *SHANK3* gene remain one of the best characterized and replicated genetic defects associated with autism spectrum disorders (ASD) in humans. We recently used CRISPR/Cas9 to target the *SHANK3* gene to generate *SHANK3* gene mutation monkeys. We found that the complete loss of *SHANK3* in the prefrontal cortex displayed a striking neuronal loss in the monkey brain, which is remarkably different from *SHANK3* knockout mouse models. Our findings suggest that *SHANK3* plays an essential role in the early development of primate brains. A live *SHANK3* mutant monkey shows a series of autism-like behavioral phenotypes, including development delay, impairments of social interaction and communication, stereotyped behaviors, and abnormal anxiety behaviors. Thus, by establishing the *SHANK3* deficient monkey model, we demonstrate for the first time that this non-human primate model could reveal the critical function of *SHANK3* and also mimic autism-like behaviors, which underscores the importance of using non-human primates to investigate the function of *SHANK3* and the pathogenesis of ASDs.

Disclosures: **T. Zhuchi:** None. **Y. Sen:** None. **Z. Hui:** None. **L. Bang:** None. **G. Xiangyu:** None. **L. Shihua:** None. **Z. Yongqing:** None. **L. Xiaojiang:** None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.12/DP01/C6

Topic: A.07. Developmental Disorders

Support: Simons Foundation

Title: A compendium of genetic and non-genetic rodent models of autism

Authors: *S. B. BASU¹, I. DAS², M. ESTÉVEZ¹, A. SARKAR¹, A. VERENDEEV¹

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Abstract: Recent advances in genetic studies have illuminated a highly complex genetic architecture underlying autism spectrum disorder (ASD). AutDB features a modular resource cataloguing multi-factorial risk factors implicated in ASD. With a systems biology approach, we incorporate diverse types of functional information related to the risk architecture underlying ASD. The animal model (AM) module of AutDB was first developed for mouse models originating from genes and CNVs associated with ASD (Kumar, 2011). Subsequently we introduced environmentally induced models to capture the full spectrum of risk factors associated with ASD, along with idiopathic models represented by inbred strains. More recently, a release of the database included rat models that are similarly categorized within a common rodent annotation framework. All data in this resource is extracted from published, peer-reviewed primary scientific reports using guidelines deeply rooted in the biology of ASD. A multilevel annotation strategy is employed for collecting behavioral, anatomical, and physiological data for each animal model. Using the data systematically annotated in AutDB we depict the intricate trends in the observations made on the phenotypes of ASD rodent models. The number of models, phenotypes, publications have increased significantly in the last three years. In contrast to the mouse models where intricate manipulation of genetic risk factors is the norm, the rat models reported in the ASD literature originate predominantly from environmental inducers. Importantly, we identify 107 genetic models and 49 induced models of ASD where various avenues of therapy including pharmaceutical agents, genetic manipulations, procedural, environmental or dietary interventions have been applied to determine their efficacy in mitigating some symptoms related to ASD. To the best of our knowledge, a complete phenotypic characterization of genetic and induced models of ASD is not accommodated in any other resource and is a unique window to examine complex meshing of diverse ASD associated risk factors.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.13/C7

Topic: A.07. Developmental Disorders

Support: Association for Psychological Sciences Student Caucus 2016 Student Grant Competition Award

Stony Brook University 2016 Undergraduate Research & Creative Activities Biology
Alumni Award

Title: Re-visiting the developmental hyperserotonemia model of autism: Stereotyped behavior and translocator protein changes

Authors: *A. S. LEE, J. DHAWAN¹, A. P. WALSH², M. A. MOORE², X. F. JIA³, Y. CHOI², E. C. AZMITIA³, A. BIEGON¹, P. M. WHITAKER-AZMITIA²

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Abstract: Previous research has reliably found high blood (hyperserotonemia) – but low brain – serotonin in autistic individuals. At early stages of development, high levels of serotonin in the blood can enter the brain of a developing fetus, causing a loss of serotonin terminals through negative feedback. During these early stages of development, serotonin stimulates astrocytes to release S100B, a critical neurotrophic factor during this period. However, when high blood level of serotonin during early development enters the fetal brain through the immature blood brain barrier, S100B release may become abnormally increased, which can stimulate microglia to release inflammatory cytokines. In fact, neuroinflammation in autistic brains has been reported in many studies, raising the question whether developmental hyperserotonemia (DHS) leads to neuroinflammation. To test this hypothesis, we used an animal model of DHS that reliably models behavioral and neurochemical changes inherent in human autism. Pregnant rats were injected on gestational day 12 with saline or 5-methoxytryptamine (5-MT; 1mg/kg) until parturition. Pups were treated with either saline or 5-MT (1mg/kg) from postnatal day 3 (P3) to P20. Post-injection, affiliative and stereotyped behaviors were examined until P20. As a first step to investigate neuroinflammation in our DHS model, we examined changes in translocator protein (TSPO) using *in vitro* autoradiography. In the 5-MT group only, pups displayed post-injection infantile seizures from P4 until P9, confirming that the drug was being delivered to the brain via the immature blood brain barrier. 5-MT treated pups showed impaired affiliative behavior and increased stereotyped behaviors, confirming low brain level of serotonin in these pups. On P22, brains of male and female offspring (n = 5/sex/treatment) were collected, cryosectioned, and processed for quantitative autoradiography of TSPO using the radioligand [¹⁸F]EPPA. There was a main effect of treatment on specific binding, whereby (contrary to our hypothesis) the 5-MT treated pups had lower binding compared to saline treated pups. The decrease in TSPO binding was notable in the dorsal raphe (DR), the major source of serotonin. This decrease in TSPO binding suggests decreased steroidogenesis in the 5-MT treated pups, which may lead to decreased neurosteroid-mediated neuroprotection in DR serotonin neurons. This decrease in neuroprotection may increase vulnerability to infantile seizures and microglial activation in 5-MT treated pups.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

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Topic: A.07. Developmental Disorders

Support: UC Davis MIND Institute IDDR U54 HD079125
NIH-NIGMS R35 GM119831
NIH-NIGMS T32-GM007377

Title: Synaptic gene dysregulation in *Chd8* haploinsufficient mice

Authors: *A. A. WADE, C. P. CANALES, I. ZDILAR, A. L. GOMPERS, T. W. STRADLEIGH, A. S. NORD

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Abstract: The gene encoding the chromatin remodeling factor (CRF), chromodomain helicase DNA binding protein 8 (*CHD8*), has one of the highest observed *de novo* loss-of-function mutation rates in patients with autism spectrum disorder (ASD). Mutations to *CHD8* have been suggested to drive pathology through global disruptions to gene expression and chromatin state in development. However, mechanisms dependent on *Chd8* function in the brain have yet to be fully elucidated and appear to extend beyond embryonic development. Recent data suggest potential postnatal-specific functions of *Chd8* in synapse development and function that could be related to cognitive phenotypes observed with patient mutations. Therefore, *CHD8* could contribute to phenotypes observed in patients through convergence between *CHD8*-dependent gene regulation and synaptic dysfunction. We performed RNA sequencing across cerebral cortex, hippocampus, and cerebellum from *Chd8* heterozygous and wild-type littermates to determine whether signatures of transcriptomic pathology observed in early development were present in adult *Chd8* mutant mice. We found differential expression of genes implicated in RNA processing and chromatin state, suggesting that some signatures observed in early development carry through later on in life. Further, using gene set enrichment analysis, we observed enrichment of genes important for neuronal maturation and synaptic function among differentially expressed genes in *Chd8* mutant mice. There were region-specific effects of *Chd8* dosage on gene expression, echoing other research suggesting context-specific *Chd8* function. From these data we conclude that impacts of *Chd8* haploinsufficiency early in development either have divergent or additive effects in adulthood or that novel consequences of *Chd8* haploinsufficiency arise in postnatal mice. Understanding the connection between stage-specific requirements for *Chd8* and ASD pathology will be important to help overcome current barriers in elucidating mechanisms underlying neurodevelopmental disorders.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

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Topic: A.07. Developmental Disorders

Support: Neurochlore

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Fellowship CIFRE-ANRT (2014/1056) to Amandine Fernandez

Title: The GABA developmental shift is abolished by maternal immune activation already at birth

Authors: *A. FERNANDEZ¹, D. GUIMOND², C. DUMON³, R. TYZIO⁴, P. BONIFAZI⁵, N. LOZOVAYA¹, N. BURNASHEV⁴, D. C. FERRARI¹, Y. BEN-ARI¹

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Abstract: Epidemiological and experimental studies suggest that maternal immune activation (MIA) leads to developmental brain disorders, but whether the pathogenic mechanism impacts neurons already at birth is not known. We now report that MIA abolishes in mice the oxytocin-mediated delivery GABA shift from depolarising to hyperpolarising in CA3 pyramidal neurons, and this is restored by the NKCC1 chloride importer antagonist bumetanide. Furthermore, MIA hippocampal pyramidal neurons at birth have a more exuberant apical arbour organisation and increased apical dendritic length than age-matched controls. The frequency of spontaneous GABAergic postsynaptic currents is also increased in MIA offspring, as well as the pairwise correlation of the synchronised firing of active cells in CA3. These alterations produced by MIA persist, since at P14-15 GABA action remains depolarising, produces excitatory action, and network activity remains elevated with a higher frequency of spontaneous glutamatergic postsynaptic currents. Therefore, the pathogenic actions of MIA include important alterations already at birth.

Disclosures: **D. Guimond:** A. Employment/Salary (full or part-time); Neurochlore. **C. Dumon:** A. Employment/Salary (full or part-time); Neurochlore. **R. Tyzio:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **P. Bonifazi:** F. Consulting Fees (e.g., advisory boards); Neurochlore. **N. Lozovaya:** A. Employment/Salary (full or part-time); Neurochlore. **N. Burnashev:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **D.C. Ferrari:** A. Employment/Salary (full or part-time); Neurochlore. **Y. Ben-Ari:** A. Employment/Salary (full or part-time); Neurochlore.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.16/C10

Topic: A.07. Developmental Disorders

Support: NIH R01 MH101584

Title: Neuronal morphology and synaptic ultrastructure in the prefrontal cortex of a SHANK3-deficient rat model of Phelan-McDermid syndrome

Authors: S. JACOT-DESCOMBES^{1,5}, E. K. SARFO^{1,6}, N. KESHAV^{1,2}, B. WICINSKI^{1,2}, W. G. JANSSEN^{1,2}, H. HARONY-NICOLAS^{3,4}, J. D. BUXBAUM^{1,2,3,4}, P. R. HOF^{1,2,4}, *M. VARGHESE^{1,2}

¹Neurosci., ²Friedman Brain Inst., ³Psychiatry, ⁴Seaver Autism Ctr. for Res. and Treatment, Icahn Sch. of Med. At Mount Sinai, New York, NY; ⁵Unit of Psychiatry, Dept. of Children and Teenagers, Univ. Hosp. and Sch. of Med., Geneva, Switzerland; ⁶City Univ. of New York, City Col. of New York, New York, NY

Abstract: Increasing evidence implicates synapse alterations in integrative brain regions as a cause of neurodevelopmental disorders. Phelan-McDermid syndrome (PMS), a monogenic form of autism spectrum disorder, is caused by deletions or mutations in the *SHANK3* gene that encodes a scaffolding protein at excitatory glutamatergic synapses. Our study explored whether there is a morphological correlate to the synaptic functional impairment, caused by the deficiency of *SHANK3*, by examining excitatory neurons in layer III of the prefrontal cortex in 5 week-old genetically modified *Shank3*-homozygous knockouts (KO), heterozygous (Het), and wild type (WT) rats. We reconstructed dendritic morphology in pyramidal neurons that were iontophoretically injected with Lucifer Yellow. We used electron microscopy to determine density of asymmetric synapses, subdividing them into perforated and non-perforated synapses and to measure the postsynaptic density (PSD) length and head diameter (HD). Apical dendrites showed a significant difference between WT and KO for dendritic length and between WT, KO,

and Het for dendrite complexity. Synapse density and PSD length were comparable among the three groups. Spine HD of Het, but not the KO rats, was increased compared to WT rats. When we analyzed HD based on synapse type, Het had higher HD in non-perforated synapses compared to WT and KO. Total PSD area was significantly increased in the Het group compared to the KO and WT. These findings represent preliminary evidence for synaptic ultrastructural alterations in the Het group, which replicates the heterozygous mutation observed in PMS. Further investigations of the mechanisms leading to altered neuronal morphology and synaptic ultrastructure in this PMS model will enable us to understand better the role of the Shank3 protein in the behavioral phenotype of PMS.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.17/C11

Topic: A.07. Developmental Disorders

Support: HIAS15002
HIAS15005

Title: Motor deficit and increased anxiety-like states in mice lacking an autism-associated gene Slit3

Authors: ***S.-M. PARK**, K. MENZEL, D. SIDIBE, C. PLACHEZ, S. HUANG
Hussman Institute For Autism, Baltimore, MD

Abstract: Slit proteins mediate axonal guidance, neuronal migration, and neuronal growth by interacting with Robo receptors, contributing to the development of neuronal connectivity and structure. Functional changes in Slit/Robo signaling has been implicated in the pathophysiology of Autism Spectrum Disorder (ASD). Altered expression of Slit or Robo receptors was reported in some individuals with ASD. A genetic variant of Slit3, one of genes encoding Slits, was also found in some individuals with ASD. However, the involvement of Slit3 mutation in the development of ASD symptoms has not been studied. Therefore, the aim of this study is to investigate behavioral changes resulting from Slit3 mutation in mice. We examined two- to four-month old male and female Slit3 knockout (KO) mice for social and repetitive behaviors, which are major diagnostic behaviors for ASD, as well as behaviors related to motor, anxiety, depression and cognition. Our data showed that Slit3-KO mice exhibited suppressed marble burying behaviors, implicating altered repetitive behavior, but normal social behaviors in the

three-chamber social tests. Furthermore, Slit3-KO mice displayed hypolocomotion in the open field test and impaired motor coordination in the rotarod test. Anxiety-like behaviors were observed mainly in female Slit3 KO mice as they displayed stronger thigmotaxis in the open field test, spent less time in the open arm of the elevated plus maze, and made fewer transitions to the light compartment in the light/dark box compared to the respective controls. No differences were observed between KO and WT mice in recognition memory in the novel object recognition test or depression-like behavior in the tail suspension test. Taken together, deletion of the Slit3 gene did not lead to ASD-like symptoms in the social behavioral domain, but it may affect repetitive behaviors. In addition, the loss of Slit3 led to aberrant motor behavior and increased anxiety-like behaviors. Motor function disruptions and anxiety are highly co-occurring symptoms in ASD. The loss of Slit3 may disrupt neural circuits required for regulating motor function and anxiety, resulting in symptoms of motor dysfunction and anxiety in ASD.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.18/C12

Topic: A.07. Developmental Disorders

Support: Hussman Foundation #15005

Title: Assessing the Role of SLIT3 in an animal model for Autism Spectrum Disorder

Authors: K. MENZEL, D. SIDIBE, *C. PLACHEZ
Hussman Inst. for Autism, Baltimore, MD

Abstract: Altered neuronal connectivity has been reported in Autism Spectrum Disorder (ASD) leading to alterations in brain function and multisensory integration. To understand how neuronal connectivity is affected in ASD this project assessed the role of SLIT3, an axon guidance molecule. SLIT proteins bind to the receptor Roundabout (ROBO) and have a role in axon guidance, cell migration, cell proliferation and differentiation of various cell types during embryogenesis. Human studies reported that SLIT3 may be associated with neurological conditions, such as major depressive disorder, schizophrenia and ASD. Taken together, these findings suggest that Slit3 may be an attractive candidate to analyze altered neuronal connectivity in ASD. Excitation/Inhibition (E/I) balance is also implicated in ASD. Since SLIT3 is involved in cell migration, we hypothesized that the GABAergic interneuron population could be affected by the loss of SLIT3 gene thus affecting the E/I balance. To this end, we used Slit3 mutant mice crossed with either GAD (Glutamate decarboxylase) 65 or GAD67-GFP mouse

lines to study GABAergic interneurons in different areas of the brain. Analysis of the GFP positive cells in GAD65/SLIT3 KO, as well as GAD67/SLIT3 KO revealed a reduced number of GABAergic interneurons in the cerebral cortex, hippocampus and cerebellum of the SLIT3 KO compared to SLIT3 WT adult mice. To identify the GABAergic interneuron population affected by the loss of Slit3 gene, we analyzed the expression of Calretinin (CaR), Calbindin (CaB) and Parvalbumin (PV) in SLIT3 adult mice. PV expression was reduced in several areas and layers of the cerebral cortex as well as the hippocampus and cerebellum of SLIT3 KO adult mice, whereas both CaR and CaB expression were not affected. Reduction of PV expression was also confirmed using western blot techniques. Interneurons are known to synchronize neuronal activity and this synchronization is essential for cortical network function. Loss of GABAergic interneurons, especially the fast spiking-PV population, in the Slit3 KO mice reveals the importance of this axon guidance molecule in the formation of these neuronal networks and provides insight into molecular pathways that may be disrupted in ASD.

Disclosures: **K. Menzel:** None. **D. Sidibe:** None. **C. Plachez:** None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.19/C13

Topic: A.07. Developmental Disorders

Support: Graduate Student Funding

Title: Assessment of motor function, motor learning, and olivary climbing fiber distribution within Developmental Hyperserotonemia rat model for Autism Spectrum Disorder

Authors: ***E. D. HOLLAND**, T. AUSTIN, L. HOUGH
Biomed. Sci., Missouri State Univ., Springfield, MO

Abstract: While Autism Spectrum Disorder (ASD) is defined by deficits in social communication and interactions, compromised motor function and delayed motor learning have been increasingly reported. Motor deficits could underpin social impairments through delayed language development, opportunities for social interaction, and nonverbal communication. One area of interest to the investigation of motor dysfunction is the cerebellum, where altered cerebellar structure and connectivity have been reported in the ASD population. Morphological and functional changes in cerebellar circuitry could disrupt motor skill development and may be linked to developmental alterations of the serotonergic system. Elevated blood serotonin in perinatal development, Developmental Hyperserotonemia (DHS), is the most consistent neurochemical finding reported in ASD, and has been implicated in the pathogenesis of the disorder. The present investigation has examined the link between DHS, cerebellar development,

and motor learning in Sprague Dawley rats. Motor learning of DHS animals was assessed through repetitive balance beam motor training and testing, with the extent of improvement over time being reflective of motor learning and motor skill rescue. Investigation of the cerebellar circuitry was performed with immunohistochemical labeling of cerebellar Purkinje cells with calbindin-D28k and olivary climbing fibers with vesicular glutamate transporter 2 (VGlut2), and assessed using confocal microscopy.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.20/C14

Topic: A.07. Developmental Disorders

Title: Calcium dynamics of astrocytes modulated by choline in the Df(h15q13)/+ mouse model of the 15q13.3 microdeletion syndrome

Authors: ***K. A. REES**, R. SRINIVASAN, U. H. WINZER-SERHAN
Dept. Neurosci. & Exp. Therap., Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX

Abstract: The 15q13.3 microdeletion (MD) syndrome has a variable phenotype in humans, but is most commonly associated with intellectual disability, epilepsy, schizophrenia, and autism. The 15q13.3MD encompasses six genes: CHRNA7, FAN1, MTMR10, TRPM1, OTUD7A, and KLF13. Haploinsufficiency of CHRNA7, which codes for the alpha7 nicotinic acetylcholine receptor ($\alpha 7$ nAChR) subunit, is thought to be a primary candidate for the development of the behavioral phenotypes in humans. A translationally relevant mouse model with a homologous deletion on the mouse chromosome 7qC, Df(h15q13)/+, was recently created, and displays behavioral features of the 15q13.3MD syndrome. The $\alpha 7$ nAChR assembles as homomeric cation channels with high calcium permeability. Studies have shown functional expression of $\alpha 7$ nAChRs on hippocampal astrocytes where they regulate astrocytic release of d-serine, a co-agonist for NMDA receptors. In this study, we used young adult male wild-type (WT) and heterozygous (HT) Df(h15q13)/+ mice to determine if calcium dynamics of astrocytes in response to $\alpha 7$ nAChR- specific drugs were altered in HT versus WT mice. To visualize the intracellular calcium activity, the genetically encoded fluorescent calcium indicator, GCaMP6f with an astrocyte specific promoter (GfaABC1D) packaged into an AAV5 viral vector, was injected into the dorsal hippocampus. Astrocyte specific GCaMP6f expression was verified by immunohistochemistry with an anti-GFP antibody and various cell-type specific markers. Two weeks after injection, hippocampal astrocytes in the CA1 stratum radiatum from acute brain slices were imaged on a confocal microscope and the somatic responses were quantified. Spontaneous calcium oscillations were observed in the soma and territories of astrocytes without

any genotypic difference. The majority of astrocytes showed a significant increase in activity compared to basal activity in response to bath application of either 10 mM choline (n= 27 cells, p=0.03) or choline in the presence of 5 μ M of the α 7 nAChR positive allosteric modulator, PNU-120596 (n=37 cells, p=0.001). In addition, co-application of PNU-120596 with choline significantly enhanced responses compared to choline application alone (p=0.002). Despite the fact that we have previously shown the HT mice have a decrease of ~50% in the number of α 7 nAChRs, there was no difference in drug-induced responses between the HT and WT mice. In conclusion, using astrocyte specific expression of GCaMP6f, we show that in hippocampal astrocytes of adult brain slices, choline, with or without PNU-120596, enhanced calcium influx into astrocytes.

Disclosures: K.A. Rees: None. R. Srinivasan: None. U.H. Winzer-Serhan: None.

Poster

032. Developmental Disorders: Animal Models of Autism

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Program #/Poster #: 032.21/C15

Topic: A.07. Developmental Disorders

Support: NIH P50MH106438
NIH P51OD011107

Title: The developmental trajectory of visual attention to social stimuli using unrestrained and noninvasive eye-tracking in infant rhesus macaques (*Macaca mulatta*)

Authors: *A. M. RYAN^{1,2,3}, A. R. LAU^{1,3}, T. MURAI⁴, C. HOGREFE³, C. S. CARTER¹, M. D. BAUMAN^{1,2,3}

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Abstract: Impairments in social behavior are a common feature of neurodevelopmental disorders, including Autism Spectrum Disorder (ASD) and schizophrenia (SZ). For example, using eye-tracking technology to measure visual attention, people with ASD and SZ consistently demonstrate atypical gaze patterns to social stimuli, which suggests that social deficits may result from altered processing of social information. Similar eye-tracking methods can be applied to preclinical animal model systems to explore the social impairments observed in neurodevelopmental disorders. Like humans, rhesus macaques (*Macaca mulatta*) use vision as their primary sensory modality and display complex social signals such as facial expressions, gestures, and vocalizations. Yet, in order to apply eye-tracking technology to animal model systems of human diseases, it is first essential to understand the typical development of visual

attention and social cognition in rhesus macaques. Here, we present longitudinal social development data on 14 male rhesus macaques that serve as a control group for a nonhuman primate maternal immune activation study. These monkeys were mother-reared, received daily access to social groups, and participated in social behavior assessments throughout development such as focal observations and eye-tracking. Eye-tracking data were collected using a modified incubator box that allowed for opportunistic sampling from unrestrained monkeys. This noninvasive approach is more comparable to the human eye-tracking experience and can be used continuously throughout development as the animals increase in size. We presented the monkeys with the same naturalistic monkey social stimuli across multiple time points from 1 month through 6 months old with additional preliminary data at 2 years old. A paired samples t-test demonstrated that the monkeys viewed the presented social stimuli for a significantly longer time when they were 6 months old than in their first three months ($p < 0.05$). As there was a three-month break in eye-tracking between 3 and 6 months of age, these results suggest that rather than habituation to the eye-tracking procedure, monkeys may develop an increased interest in social stimuli during this early critical period of social development. Further exploratory analyses of how our other measures of social behavior and cognition relate to visual attention as assessed through eye-tracking can help to both understand the development of social cognition in rhesus macaques as well as how eye-tracking in nonhuman primates can translate to our understanding of potential causes of and treatments for neurodevelopmental disorders.

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Poster

032. Developmental Disorders: Animal Models of Autism

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Program #/Poster #: 032.22/C16

Topic: A.07. Developmental Disorders

Support: NSFC 91232301
NSFC 31471041

Title: Foxg1 regulates the development of cortical somatostatin-expressing interneurons

Authors: *D. CHEN, Y. NI, Y. SU, C. ZHAO
Southeast Univ., Jiangsu, China

Abstract: The subpopulation of somatostatin-expressing interneurons (SST-INs) play important roles in cortical circuits. Dysfunction of SST-INs has been reported to be closely related to neuropsychiatric disorders such as epilepsy and depression. Several subtypes including SST⁺/CR⁺, SST⁺/NPY⁺, SST⁺/Reelin⁺ have been identified among the SST-INs population.

However the mechanism underlying the development of SST-INs remains unclear. Patients with *Foxg1* mutations suffer from epilepsy, severe anxiety and autism, suggesting a pivotal role for *Foxg1* in interneuron development. Previously we have demonstrated that *Foxg1* is required for the migration of cortical interneurons, the role of *Foxg1* in distinct subpopulations of interneurons remains poorly understood. To get insight to how the development of SST-INs is regulated, *Foxg1* was specifically removed by crossing *SST-cre* with *foxg1^{fl/fl}*. Disruption *Foxg1* in SST-INs leads to a substantial decreased number of SST-INs that may be a consequence of reduced proliferation of interneuron progenitors in the ganglionic eminence at early developmental stages. More SST-INs populate in the deeper cortical layer rather than in the superficial layers in *Foxg1* adult mutants. Interestingly, by genetic cell tracing, we have found the ratio of subtypes of SST-INs is altered. The percentages of SST⁺/NPY⁺ and SST⁺/Reelin⁺ subtypes among SST-INs are obviously increased, meanwhile the percentage of SST⁺/CR⁺ is reduced, suggesting a cell fate switch after *Foxg1* deletion. Consistent with their abnormal molecular profiles, mutant SST-INs exhibits alteration of the electrophysiological firing properties among subclasses. Behavior analysis shows *Foxg1* mutants have impaired cognitive function and social interaction, and exhibit depression-like behavior. Treatment with ketamine, which has rapid antidepressant effect, improves the depression-like behavior of our SST-IN deficient mice. These findings define a previously unknown role for *Foxg1* on the development of SST-INs and provide a new insight into *Foxg1*-related disorders.

Disclosures: D. Chen: None. Y. Ni: None. Y. Su: None. C. Zhao: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.23/C17

Topic: A.07. Developmental Disorders

Title: Impaired behavioral flexibility in a mouse model of autism spectrum disorder

Authors: *M. YUN^{1,2}, J. SHIN^{1,3}, E. KIM^{1,2}, M. W. JUNG^{1,2}

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Abstract: We hypothesize that impaired behavioral flexibility might underlie an array of symptoms associated with autism spectrum disorder (ASD), especially repetitive and restricted behavior. Reversal learning is a simple test for behavioral flexibility, and previous studies have shown that ASD patients and BTBR T+tf/j (ASD model) mice are impaired in probabilistic reversal learning. As an attempt to develop an efficient behavioral paradigm to test behavioral

flexibility in ASD model mice, we tested Shank2 knockout (Shank2-KO) mice in a probabilistic reversal learning task under a head-fixed condition. Two different odor cues were presented to a head-fixed mouse and paired with a reward (water) or a punishment (air puff) each with 75% probability. Head fixation prevented Shank2-KO mice from emitting abnormal hyper-excitable behaviors, such as excessive grooming and jumping, but Shank2-KO mice showed normal licking behavior in response to water delivery. Both Shank2-KO and wild type mice showed higher anticipatory licking responses to the reward-predicting than punishment-predicting cues, indicating intact learning of cue-outcome contingency in both animal groups. However, upon the reversal of cue-outcome contingency, it took much longer for Shank2-KO than wild type mice to show higher anticipatory licking responses to the new reward-predicting cue. These results suggest our probabilistic reverse learning task as a potentially useful behavioral paradigm for testing behavioral flexibility in ASD model mice.

Disclosures: M. Yun: None. J. Shin: None. E. Kim: None. M.W. Jung: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.24/C18

Topic: A.07. Developmental Disorders

Support: Grant from the Fondation pour la Recherche Médicale (FRM)

Title: Environmental models of autism spectrum disorder display fine motor deficits and sex specific restricted neuronal loss

Authors: *E. MATAS, T. AL SAGHEER, O. HAÏDA, A. BALBOUS-GAUTIER, M. FRANCHETEAU, P.-O. FERNAGUT, M. JABER
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Abstract: Motor comorbidities such as hypotonia, motor apraxia and dystonia affect patients with autism spectrum disorder (ASD) which suggest that motor function and associated brain areas may be affected in this illness. Fine and gross motor skills depend on motor cortex, basal ganglia, and cerebellum function. The cerebellum has been consistently reported with abnormalities in ASD and may be associated with motor skills dysfunctions as well as social deficits observed in this disease. Indeed, the most reliable outcome from postmortem Human studies is the loss of Purkinje cells (PCs) in this brain region. However, the contribution of the cerebellum and other brain areas implicated in motor skills in ASD remains poorly understood. The aim of the study was to characterize fine motor dysfunctions and underlying cellular and molecular deficits in 2 mouse models of ASD. In this study we utilized 2 mouse models of ASD: (1) Prenatal exposure to valproic acid (VPA) at E12.5; (2) Prenatal exposure to

polyinosinic:polycytidylic acid (poly I:C) at E12.5. We used the three chambers test to evaluate the social behavior of the models of ASD. We explored fine motor functions in these models with the challenging beam test and the gait analysis. Stereological analysis was performed to quantify neurons in the cerebellum (PCs), the striatum and the motor cortex. In addition, these brain regions were collected for real time polymerase chain reaction and western blot analysis. Blinded experiments were performed with both males and females at P35-45. This study revealed that in both VPA and poly I:C models of ASD only males show social deficits. However, we found that fine motor functions were affected in both males and females in the VPA model. Conversely, only males prenatally treated with poly I:C showed fine motor dysfunctions. Sex specific and restricted loss of neurons in the cerebellum (PCs) and the motor cortex was observed in both models. Interestingly, correlation analysis highlighted strong associations between motor deficits, social behavior and PCs loss. In addition, our results show a significant increase of mammalian target of rapamycin (mTOR) phosphorylation in the motor cortex and the cerebellum in males prenatally exposed to VPA. Altogether these results suggest that sex may be a protective factor to the risk of developing ASD as females prenatally exposed to VPA and poly I:C did not display social deficits. Discrepancy observed between both models in fine motor behaviors may be useful to a more accurate diagnosis of ASD. Eventually, the observed cell loss within the cerebellum and the motor cortex may be mediated through protein synthesis and/or autophagy dysfunctions in the VPA model.

Disclosures: **E. Matas:** None. **T. Al Sagheer:** None. **O. Haïda:** None. **A. Balbous-Gautier:** None. **M. Francheteau:** None. **P. Fernagut:** None. **M. Jaber:** None.

Poster

032. Developmental Disorders: Animal Models of Autism

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Topic: A.07. Developmental Disorders

Support: APF/COGDOP Graduate Student Scholarship

UF Department of Psychology Gerber Graduate Student Research Award

UF Department of Psychology Jacquelin Goldman Spring Scholarship

Title: Habitual responding in a mouse model of restricted, repetitive behavior: Associations with basal ganglia morphology

Authors: ***L. CURRY-POCHY**¹, J. FEINSTEIN¹, B. YAFFE¹, M. H. LEWIS²

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Abstract: Restricted, repetitive behavior (RRB) is diagnostic for autism spectrum disorder (ASD) and characteristic of many neurodevelopmental, psychiatric, and neurological disorders. RRB in ASD includes repetitive motor behavior and behaviors reflecting resistance to change and insistence on sameness. Previous work in other disorders (e.g., obsessive-compulsive disorder, Tourette syndrome) has linked RRB to deficits in goal-directed behavior and a propensity to engage in habitual responding. The dynamic dual-process framework of goal-directed and habitual behavior has largely not been applied to RRB in neurodevelopmental disorders like ASD. We examined the relationship between RRB and habitual responding in an animal model of RRB using two methods to induce habit, overtraining (study 1) and a random interval schedule (RI) of reinforcement (study 2). We hypothesized that habitual responding would have differential consequences on reversal learning, which was used as a measure of resistance to change. Using C58 mice, which exhibit repetitive behavior, and control C57BL/6 mice, we independently assessed repetitive behavior, habitual responding, and contingency reversal learning. In study 1, C58 and C57BL/6 mice were randomly assigned to a training or overtraining group. Overtraining induced habitual responding in both strains albeit with different consequences for reversal learning. Overtrained C58 mice exhibiting habitual responding showed significant reversal learning deficits compared to controls. The RI schedule of reinforcement also induced habitual responding in both strains. C58 mice, however, showed a deficit in the ability to suppress responding during omission trials compared to C57BL/6 mice. Taken together, inducing habitual responding resulted in contingency reversal learning deficits only in mice exhibiting repetitive motor behavior. Moreover, strain differences in dendritic morphology were assessed in basal ganglia nuclei. The findings described here suggest targeted developmental interventions and treatment.

Disclosures: **J. Feinstein:** None. **B. Yaffe:** None. **M.H. Lewis:** None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

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Program #/Poster #: 032.26/C20

Topic: A.07. Developmental Disorders

Support: FAPESP Grant 2016/01154-0
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Title: Reduced social motivation oxytocin signaling are involved on social behavior impairment in rats submitted to neonatal status epilepticus

Authors: ***R. M. CYSNEIROS**¹, F. T. RIBEIRO², M. SERRA-AZUL², F. LORENA²

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Abstract: Neonatal status epilepticus (SE) in rats is a model to study mechanisms underlying social impairment in Autism Spectrum Disorder (ASD). We previously demonstrated that a single neonatal SE in rats produces low preference by novelty and deficit in social discrimination with no changes in cognition function. Endocannabinoid and oxytocin play important roles on social behavior, as motivation, reward processes and social recognition memory. The role of endocannabinoid and oxytocin on social behavior impairment was evaluated in adults male Wistar rats subjected to pilocarpine-induced neonatal SE (380mg/kg, ip) at postnatal day 9 (PN9). At P60 both groups were injected with JZL195 (0.01 mg/kg, i.p.), an inhibitor of FAAH and MAGL, enzymes responsible by endogenous cannabinoids metabolism. Two hours later, the memory of social recognition and locomotor activity (LA) were evaluated. Experimental animals exhibited reduction in social investigation toward an unfamiliar conspecific ($F(1,18)=5.399$; $p=0.032$). JZL treatment reduced time of investigation only in control group ($F(1,18)=4.28$; $p=0.05$), with no effect in social discrimination. For total locomotion, a significant effect of interaction between factor (group x treatment, $F(1,7)=8.99$; $p=0.02$) was observed, revealing a reduced LA only in experimental animals ($t=3.01$, $p<0.05$). mRNA expression for CNR1 gene did not differ between groups in none the brain structures: hippocampus ($t(6)=0.05$; n.s.), prefrontal cortex, ($t(6)=1.3$; n.s.), striatum ($t(6)=0.1$; n.s.) or amygdala ($t(6)=0.8$; n.s.). Protein expression for CNR1 did not differ between groups: hippocampus ($t(8)=1.8$; n.s.), prefrontal cortex ($t(8)=1.0$; n.s.), striatum ($t(8)=0.08$; n.s.) or amygdala ($t(8)=0.4$; n.s.), but a significant decreased for oxytocin receptor was observed in hippocampus of experimental animals ($t=2.45$, $p=0.034$). Oxytocin signaling in hippocampus may be involved in social discrimination impairment in this model. The lack of effect the enhancement of endocannabinoid signaling on social impairment in experimental animals, suggest that SE also affected appetitive motivation for social interaction. We also raised the assumption that brain network involved in social behavior is more vulnerable to SE than that involved with cognitive function

Disclosures: R.M. Cysneiros: None. F.T. Ribeiro: None. M. Serra-Azul: None. F. Lorena: None.

Poster

032. Developmental Disorders: Animal Models of Autism

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Topic: A.07. Developmental Disorders

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Title: Social skills in autism spectrum disorders relate with connectivity changes in the limbic system: An MRI study in *Nf1*^{+/-} mice

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Abstract: Autism spectrum disorders (ASD) are a range of neurodevelopmental disorders. The ASD phenotype is characterized by reduced sociability, communication deficits and stereotyped behavior. Diverse mice models have been useful in understanding some of the associated neurobehavioral features. However, studies targeting neural correlates of social/emotional phenotypes in ASD are still sparse and controversial. Amygdala disruptions have been associated to poorer social learning and behavioral problems, but other limbic structures need to be considered.

The *Nf1*^{+/-} mouse model has been used to study executive, language and social deficits of ASD. Here, we study connectivity in *Nf1*^{+/-} and control mice (mean diffusivity MD; fractional anisotropy FA) in structures of the limbic system beyond the amygdala, and how they predict social skills. DTI data were acquired *in vivo* with a 9.4 T scanner. Average MD and FA values were computed on the regions of interest (Fig 1A). Genotype differences were assessed (Student's T-test, $\alpha=5\%$, with outliers exclusion and FDR correction, $Q=5\%$). Pearson's correlations between pairs of structures for MD/FA values were implemented. Sociability tests analyzed the fraction of time the mice spend with novel mice (%TNM) related to familiar mice, and it was related to MD/FA measurements.

We found an increase in MD for *Nf1*^{+/-} mice in all the ROIs. FA was higher in *Nf1*^{+/-} mice only for the neocortex (Fig 1B). MD correlations were specific for *Nf1*^{+/-} mice, with marked involvement of the PAG (Fig 1C). Analysis of %TNM revealed that *Nf1*^{+/-} mice did not discriminate between familiar and novel mice, and this measure is positively correlated with FA in the cingulum (CIN) and hypothalamus (HYP) only in control mice (Fig 1D).

We show that connectivity patterns in the limbic system are compromised in ASD, and that they are associated with behavioral/social deficits. Involvement of PAG in *Nf1*^{+/-} mice suggests an underlying mechanism for atypical pain perception and social cognition. Connectivity alterations in the CIN and HYP may also play a relevant role in the social phenotype of ASD.

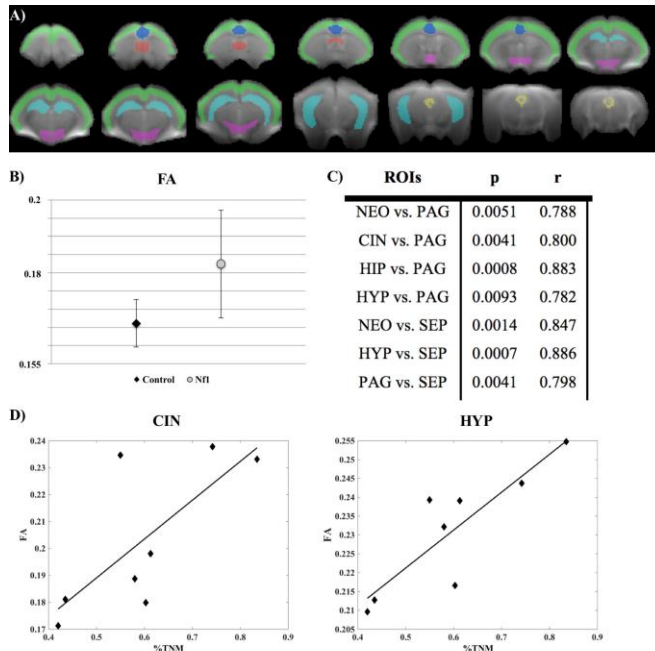


Fig 1. A) Identification of the Regions of interest (ROIs): neocortex (NEO, green), cingulum (CIN, blue), septum (red), hypothalamus (HYP, magenta), hippocampus (HIP, cyan) and periaqueductal gray (PAG, yellow). B) Fractional anisotropy (FA) at the NEO was significantly higher in *Nf1*^{+/-} mice ($p=0.0048$, $t=-3.46$). C) Mean diffusivity (MD) correlations that were only significant in *Nf1*^{+/-} mice. D) Correlations between social skills (%Time with novel mice) and FA were significant at CIN ($p=0.0392$, $r=0.731$) and HYP ($p=0.0054$, $r=0.866$) only for control mice.

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Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 032.28/C22

Topic: A.07. Developmental Disorders

Title: Do gestational SSRIs lead to an increase in autism symptoms? A rat model using perinatal paroxetine

Authors: *H. GARMAN, S. KWON, M. MOORE, A. RUSSO, R. PARSONS, P. WHITAKER-AZMITIA

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Abstract: Autism Spectrum Disorder (ASD) symptoms respond best to therapies when diagnosis is early in development. Thus identifying risk factors is crucial. As one of the earliest-developing systems in the mammalian brain, serotonin plays a central role in brain development. Past studies

have suggested the link between perinatal exposure to antidepressants and subsequent birth of children on the autism spectrum. Disruption of serotonergic development through maternal use of SSRIs, such as paroxetine, can leave permanent alterations in brain circuitry and consequently contribute to symptoms of ASD. The current study examined effects of perinatal paroxetine exposure in a rat model of ASD. Six timed-pregnant Sprague-Dawley dams were randomly assigned into treatment and control groups (3 each). Treatment group dams were treated with 10 mg/kg of paroxetine via water daily (GD 12-PND19; dosage tapered PND9-18 by -1mg/kg/day). Control groups dams received drinking water only and water intake was monitored daily for both groups. Developmental milestones were recorded; in addition, eleven behavioral tasks were conducted to test for motor coordination, maternal and littermate bonding, habituation to novel environment, learning and memory, social affiliation preference and finally, fear conditioning. Results showed that the treatment group had premature deaths (3 out of 33), lower weight at birth ($t(66)= 9.481, p < .001$), delayed eye opening ($t(66)= 3.667, p < .001$), took longer to right themselves during motor development task ($t(66) = 2.639, p < .05$) compared to the control group. Additionally the treatment group showed deficits in social bonding with littermates ($t(58)= 7.6, p < .001$), deficits in learning fear conditioning ($t(6)= 2.368, p < .056$) and more repetitive behaviors ($t(66)= 3.0, p < .001$) compared to the control group. The current study reflects possible behavioral and morphological consequences of perinatal SSRI exposure in exhibiting symptoms of ASD. The behavioral data demonstrates the extent to which a disruption in the developing serotonergic system via perinatal SSRI exposure is associated with deficits in social bonding, more frequent repetitive behaviors, and delayed motor development, relative to those who had not been exposed to SSRIs. In addition, SSRI exposure lead to premature deaths in 3 out of 33 pups in the treatment group, a 9% mortality rate. This risk of infantile death is consistent with both animal and human studies. Morphological analyses of SERT and neuroinflammation (using markers of activated microglia) via autoradiography and a more thorough data analysis of sex differences are currently underway.

Disclosures: H. Garman: None. S. Kwon: None. M. Moore: None. A. Russo: None. R. Parsons: None. P. Whitaker-Azmitia: None.

Poster

032. Developmental Disorders: Animal Models of Autism

Location: SDCC Halls B-H

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Program #/Poster #: 032.29/C23

Topic: A.07. Developmental Disorders

Title: Differences in female BTBR T+ tf/J and C57BL/6J mice on stereotyped repetitive behaviors associated to autism spectrum disorder

Authors: A. PAHUA, M. ZARATE, J. TAYLOR, P. FLORES, M. SEEGER, *D. A. AMODEO
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Abstract: Across many studies we find that many more males than females show symptoms of autism spectrum disorder (ASD). More recent studies suggest that this may be due to how we characterize symptoms with a bias towards how they are expressed in males. Thus this gender discrepancy may not be as large as previously reported. In the ASD animal model literature, the need to test female mice is often ignored. We have repeatedly demonstrated that male BTBR T+tf/J (BTBR) mice express increased repetitive grooming, increased marble burying and impairments in behavioral flexibility, results supported by findings in several other laboratories. In the current experiment we conducted these same behavioral tests in both BTBR and C57BL/6J control female mice. Female C57BL/6J and BTBR mice were tested in all behavioral measures. Results demonstrate that female BTBR mice do not groom more than female C57BL/6J mice. This is because control female C57BL/6J mice tend to groom at much higher rates than those found in C57BL/6J male mice. Alternately, Female BTBR mice showed increased marble burying and impairments in behavioral flexibility compared to female C57BL/6J mice. These particular findings are similar to those found in studies only testing male BTBR mice. Present findings highlight the need to revisit our clinical measures of RRBs in ASD to effectively design measures that are sensitive to gender differences in the manifestation of RRBs. Overall results highlight the need to include female mice in rodent model studies of ASD.

Disclosures: A. Pahua: None. M. Zarate: None. J. Taylor: None. P. Flores: None. M. Seeger: None. D.A. Amodeo: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.01/C24

Topic: A.09. Adolescent Development

Support: Keck

Title: Chronic periadolescent methylphenidate administration decreases gpr54 gene expression in the preoptic area of female rats

Authors: *F. A. GUARRACI¹, N. LE¹, N. MEBANE², A. HOLLEY³, A. C. GORE³

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Abstract: Methylphenidate (MPH) is a catecholamine reuptake inhibitor that is commonly prescribed to children and adolescents diagnosed with Attention-Deficit Hyperactivity Disorder.

Although there has been a recent increase in MPH prescriptions, the effects of childhood-MPH exposure have not yet been fully elucidated. We have previously shown that chronic periadolescent administration of MPH alters puberty onset, estrous cyclicity, and reproductive behavior in female rats. The current study investigated the effects of chronic periadolescent administration of MPH on gene expression in areas of the hypothalamus and forebrain involved in the development of reproductive physiology and behavior: preoptic area (POA), arcuate nucleus (ARC), and nucleus accumbens (NAc). Male (n=20) and female (n=23) rat pups received MPH (2.0 mg/kg, i.p.) or saline twice daily for 16 days between postnatal day (PD) 20-35. Brain tissue was sampled when subjects were approximately PD 65. Real-Time PCR was used to measure relative gene expression of GPR54 in the POA, ER-alpha and ER-beta in the ARC, and D₁ and D₂ receptors in the NAc. MPH had no effect on relative gene expression in the ARC or NAc in either male or female rats. However, chronic periadolescent MPH exposure significantly decreased relative expression (70%) of the kisspeptin receptor (GPR54) only in adult female rats when compared to females that received periadolescent saline injections. These results suggest that chronic periadolescent MPH administration, similar to a therapeutic dose prescribed to girls, could have long-term effects on the neuroendocrine system, disrupting both puberty onset and reproductive cyclicity in female rats by downregulating kisspeptin receptor expression in the POA.

Disclosures: F.A. Guarraci: None. N. Le: None. N. Mebane: None. A. Holley: None. A.C. Gore: None.

Poster

033. Adolescent Development: Animal Models I

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Program #/Poster #: 033.02/C25

Topic: A.09. Adolescent Development

Support: R01 DA034185
R01 MH101183
F32 DA043308

Title: Microglial elimination of dopamine receptors defines sex-specific nucleus accumbens development and social behavior during adolescence

Authors: *A. M. KOPEC¹, C. J. SMITH¹, N. R. AYRE¹, S. C. SWEAT², S. D. BILBO¹
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Abstract: Adolescence is a developmental period in which the mesolimbic dopaminergic 'reward' circuitry of the brain, including the nucleus accumbens (NAc), undergoes significant

developmental plasticity. Dopamine D1 receptors (D1rs) in the NAc are critical for social behavior, but how these receptors are regulated during adolescence is not well understood. We demonstrate that microglia and complement-mediated phagocytic activity shapes NAc development by eliminating D1rs in males, but not females, during adolescence. Moreover, immune-mediated elimination of D1rs is required for normal developmental changes in adolescent social play behavior in males. Interestingly, though immune processes are not regulating D1r levels in females, perturbing the complement-microglial relationship locally in the NAc also increases social play behavior in females, suggesting that an as yet undetermined immune process is occurring in the female NAc during adolescence to mediate social behavior. These data demonstrate for the first time that microglia and complement-mediated immune signaling (i) participate in adolescent brain development in the NAc, (ii) are engaged in a sex-specific manner, and (iii) are causally implicated in developmental changes in behavior, and have broad implications for understanding the adolescent critical period of development, the molecular mechanisms underlying social behavior, and sex differences in brain structure and function.

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Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.03/C26

Topic: A.09. Adolescent Development

Support: College of Science, NUI Galway postgraduate fellowship

Title: The effects of gestational exposure to SSRI antidepressants in anxiety tests in rat offspring

Authors: *N. A. DESANCTIS^{1,2}, J. P. KELLY^{1,2}

¹Dept. of Pharmacol. and Therapeut., Natl. Univ. of Ireland, Galway, Galway, Ireland; ²Galway Neurosci. Ctr. NCBES, Galway, Ireland

Abstract: Introduction The most commonly prescribed psychotropic drugs in pregnancy are SSRI (selective serotonin reuptake inhibitor) antidepressants¹. Passing the placental barrier, clinical gestational exposure is associated with lower birth weights, preterm birth and developmental delays². This study examined the effects of four clinically used SSRIs, paroxetine (PRX), sertraline (SERT), citalopram (CIT), and fluoxetine (FLX), *in utero* using a clinically relevant approach developed in our laboratory³ and appropriate doses informed by previous findings⁴.

Methods Female Sprague-Dawley rats (approx. 4 months old) were mated and single housed.

From gestation day 7 until littering, dams received either vehicle, 1.25, 2.5, or 5 mg/kg PRX, 2.5, 5 or 10 mg/kg SERT or CIT, or 2.5 mg/kg FLX via oral gavage (n=9-13/group). Maternal weights were recorded. Pup characteristics such as litter size, sex ratio and mortality were noted following littering. After weaning pups were group housed. At postnatal day (PND) 28, 56, and 84 offspring were tested in the elevated plus maze (EPM) and open field (OF) to assess anxiogenic behaviour. Pup data was assessed for differences in sex. Data were analysed using ANOVA or Kruskal-Wallis, followed where appropriate by *post hoc* SNK test. FLX data was analysed via Independent Sample T-test or Mann-Whitney U test. Pup mortality was analysed via Chi-Squared test; $p < 0.05$ was deemed statistically significant.

Results During gestation, SERT (10 mg/kg) significantly reduced maternal weight gain and food consumption. At birth there were no differences in litter size or sex ratio. However, there was a significant increase in mortality within the week following littering for PRX (2.5, 5 mg/kg) and SERT (10 mg/kg) dams. An effect of sex was found in all treatments for PND 1 bodyweight. FLX (2.5 mg/kg) significantly reduced open arm time in the EPM for males at PND 56. A significant decrease in inner zone time was found in the OF for males at PND 84 with SERT (5, 10 mg/kg) and CIT (2.5, 5 mg/kg) groups. FLX (2.5 mg/kg) significantly reduced inner zone time in the OF for females at PND 56 and 84.

Conclusions Overall, the data demonstrate that at pharmacological doses, both PRX and SERT have profound effects on neonatal mortality in the rat. Furthermore, an anxiogenic effect was detected in the EPM and OF for pups exposed to SERT, CIT and FLX. Such findings in an animal model could have important implications for prescribing SSRI antidepressants during pregnancy.

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4. DeSanctis. N.A. *et al.* (2016) *E Br J Pharm* 2016

Disclosures: N.A. DeSanctis: None. J.P. Kelly: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.04/C27

Topic: A.09. Adolescent Development

Title: Enrichment during adolescence differently effects evoked activity in entorhinal cortex following a single enriching experience in early adulthood

Authors: H. GODFREY, H. C. LIESEGANG, *M. C. ZRULL
Psychology, Appalachian State Univ., Boone, NC

Abstract: Effects of experiences during adolescent certainly influence, and may persist, into young and later adulthood. For adolescent rats, environmental enrichment (EE), or the opportunity to interact with same-sex conspecifics in a unique environment containing novel objects, allows for informal learning about spatial, social, and physical features of the environment. EE can have profound and lasting effects on the brain regions dedicated to learning and memory such as the hippocampal formation (HF) and entorhinal cortex (EC). EC Layers 2 and 3 relay neural signals to HF, and EC receives HF output in Layers 5 and 6. We examined the effect of a single EE session on EC activity in rats with, or without, a prior history of periodic EE. Thirteen Long-Evans rats were exposed to periodic EE between postnatal days (pnd) 30 and 60 and 14 controls were not. During 90-min, daily EE sessions, same-sex enriched rats were placed into enclosures with ramps, platforms, and routinely changed objects. Control rats were not enriched but were handled, and all rats were housed as same-sex triples. Prior to sacrifice between pnd 75 and 78, 7 enriched (EE+EE) and 7 control (No+EE) rats experienced a final, acute EE session and other rats did not (EE+No, No+No, n=6 and 7). Brain tissue was processed to visualize the neural activity marker c-FOS using floating section immunohistochemistry, and activated neurons were quantified in EC regions using digital microscopy and stereological technique. For EC Layers 2 and 3, EE+EE, EE+No, and No+No groups exhibited similar c-FOS+ neuron counts with brains from No+EE rats showing increased numbers of activated neurons (+371%, $p < .001$). In contrast, EC Layers 5 and 6 in tissue from EE+EE and No+EE rats showed 200% more c-FOS+ neurons than from rats not experiencing a single, final EE session as young adults ($p < .001$). The increased neural activity in EC Layers 2 and 3 of No+EE rats indicates that only current novel experience seems to influence the extent of input relayed to HF from neocortex. Neurons of EC Layers 2 and 3 are not as active in rats with a prior history of similar experience (i.e., EE+EE and EE+No groups). However, a current enriching experience enhances activity of EC Layers 5 and 6 neurons for rats with and without EE history. Together, these results provide an expected illustration of input to and output from a model memory system. While input to hippocampus, the integrating component of the system, is influenced primarily by current experience, output back to the cortical part, the storage component, of the memory system is responsive to current events and, at least, related aspects of an animal's history.

Disclosures: H. Godfrey: None. **H.C. Liesegang:** None. **M.C. Zrull:** None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.05/C28

Topic: A.09. Adolescent Development

Title: Alpha5-GABA_ARs specifically regulate synaptic transmission from somatostatin-expressing interneurons to excitatory neurons in developing visual cortex

Authors: *J. CAO, Y. YU, Y. FU
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Abstract: It is well known that GABA_A receptors mediate the majority of inhibitory synaptic interactions in the mammalian cortex. Earlier studies have indicated clear changes in GABA_A receptor subunit expression during early postnatal development. Unlike other subunits, the expression of $\alpha 5$ subunit showed significantly decreased during early postnatal development. However, the specific role during neocortical inhibitory microcircuits development is still unclear. Here, we systematically investigated the functional role of $\alpha 5$ -GABA_ARs in synaptic maturation of somatostatin-expressing interneurons in visual cortex. We found IAalpha5 (5 μ M, specific $\alpha 5$ inverse agonist) significantly reduced the peak amplitude of SST-IN to PC uIPSCs by ~25%. Interestingly, IAalpha5 had no significant effect on the peak amplitude of uIPSCs from SST-INs to other types of interneurons. Further experiments using immune-gold EM demonstrate the existence of $\alpha 5$ -GABA_ARs at single SST-IN to PC synapses. Unexpectedly, the relative reduction induced by IAalpha5 at P12-13 were much larger than that at P14-15, suggesting that $\alpha 5$ -GABA_ARs-mediated synaptic transmission at SST-IN to PC synaptic connections during a narrow time window. Altogether, we discovered the specific role of $\alpha 5$ -GABA_ARs during the maturation of somatostatin-expressing interneurons to excitatory neurons in developing visual cortex.

Disclosures: J. Cao: None. Y. Yu: None. Y. Fu: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.06/C29

Topic: A.09. Adolescent Development

Support: Research grant UMO-2016/21/B/N24/00203 - National Science Centre (Poland)
Statutory funds of the Institute of Pharmacology PAS (Poland)

Title: The effects of maternal high carbohydrates diet on melanocortin-4 receptor levels in the brain of male and female rat offspring

Authors: *K. MUDLAFF, D. GAWLINSKI, E. PRZEGALINSKI, M. FILIP
Inst. of Pharmacology, Polish Acad. of Scien, Krakow, Poland

Abstract: Background: Pre- and postnatal factors influence the brain development and function, impacting health outcomes with particular relevance to neurodevelopmental diseases. Both

human and animal studies prove the relationship between the composition of the mother's diet and the risk of the appearance of behavioral disorders. Studies indicate that the diet consumed in adolescence and adulthood has a huge risk of developing diseases such as obesity, anxiety, psychosis and depression. The central melanocortin system, particularly the melanocortin-4 (MC-4) receptor subtype, plays an important role in the control of physiological functions and in the pathogenesis of the above disturbances. Environmental factors, such as maternal diet, nutrient intake or feeding behaviors, can modulate the association of MC-4 receptors gene with obesity.

Aim: We investigate the effects of maternal high carbohydrates diet on the level of MC-4 receptors in male and female offspring rat brain.

Methods: Wistar rat dams were maintained ad libitum either on high carbohydrates diet (HCD, carbohydrates 70%) or standard rodent chow (control group) during gestation and 21 days of lactation. After this period, the onset were separated with full access to standard chow. At 63 postnatal day the offspring (n=8/group) was sacrificed through decapitation, and the brains were rapidly removed. The prefrontal cortex, nucleus accumbens, dorsal striatum, hypothalamus and ventral tegmental area were isolated. Alternations in MC-4 receptors were evaluated by enzyme-linked immunosorbent assay (ELISA) in extracted synaptosomal fraction.

Results: Our data show a significant increased level of MC-4 receptors in the nucleus accumbens ($p < 0.001$) and in ventral tegmental area ($p < 0.05$) in male offspring on HCD. Moreover, for both male and female offspring which mothers were fed on HCD, we demonstrate a rise in MC-4 receptors level in the hypothalamus synaptosomal fraction ($p < 0.01$).

Conclusion: Our data suggest significant changes in the level of MC-4 receptors in offspring rats which mothers were fed on HCD during gestation and lactation. The in vivo functional tests should be performed to verify the outcome.

Disclosures: **K. Mudlaff:** None. **D. Gawlinski:** None. **E. Przegalinski:** None. **M. Filip:** None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.07/C30

Topic: A.09. Adolescent Development

Support: NIH Grant R01MH086507 to KY Tseng
NIH Grant R01MH105488 to KY Tseng

Title: Differential regulation of input-specific plasticity in the prefrontal cortex by 2-AG and AEA

Authors: *H. M. MOLLA^{1,2}, D. R. THOMASES¹, K. Y. TSENG¹

¹Anat. and Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; ²Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Prefrontal cortex (PFC) maturation during adolescence is characterized by structural and functional changes, which involve the remodeling of GABAergic and glutamatergic transmission. Endocannabinoid levels (2-AG and AEA) in the PFC also undergo distinct changes during adolescence. What remains unknown is how each endocannabinoid modulates glutamate and GABA transmission in the PFC during the transition to adulthood. To address this, we conducted local field potential recordings *in vivo* and examined how manipulations of the endocannabinoid system affects PFC responses to basolateral amygdala (BLA) and ventral hippocampal (vHipp) stimulation. Pharmacological elevation of PFC 2-AG and AEA levels exert differential control over LTP and LTD from BLA and vHipp inputs. Interestingly, both endocannabinoids 2-AG and AEA are recruited by vHipp-evoked LTD. However, only 2-AG mediates the inhibitory effect of CB1R signaling of both BLA- and vHipp-evoked LTP. Together, these results show that 2-AG and AEA differentially regulate PFC plasticity and the gain of afferent drive that arises from BLA and vHipp inputs.

Disclosures: H.M. Molla: None. D.R. Thomases: None. K.Y. Tseng: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.08/C31

Topic: A.09. Adolescent Development

Support: Marc U*Star NIH 5T34GM11812

Title: Effects of adolescent sucrose on resistance to punished cocaine in adult male and female rats

Authors: *R. PARMAR, M. COBB, R. ARANGO, M. WRIGHT, J. PARENT, I. C. SUMAYA, A. M. GANCARZ

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Abstract: In humans, adolescence is a transition between childhood and adulthood accompanied by significant behavioral and neural development (Ernst et al., 2006). Environmental challenges during this crucial time of neural plasticity could potentially result in dire neurodevelopment and behavior consequences in adulthood. It is known that exposure to drugs of abuse during adolescence increases future susceptibility to drug addiction in adulthood, yet little is known about exposure to other natural stimuli that may also alter functioning of the mesolimbic

dopamine circuitry and their effects on drug abuse in adulthood. Given that natural and drug reinforcers activate the same neural circuitry (Wise & Rompe, 1989), this pathway may also be responsible for such increases in reactivity to natural reinforcers (sucrose) during the adolescent period. Further research is needed to understand exposure to naturally rewarding stimuli during the adolescent period that may alter functioning and behavior. Here, we seek to understand how exposure to sucrose could alter behavior in adulthood. In order to test this, male and female adolescent rats (PND 28-42) were exposed to either 10 % noncontingent sucrose or water delivery in fourteen 30 min sessions in operant settings. In adulthood, rats were fitted with chronic indwelling jugular catheters and allowed to recover (PND 51-53). Rats were then tested for cocaine self-administration (PND 54-60). During this phase, rats emitted a snout poke response to receive 1.0 mg/kg/infusion of cocaine according to a Fixed Ratio 1 (FR1) schedule of reinforcement. The schedule was increased to FR5 across the 7 days of testing. Following this phase, rats were then tested for resistance to punished cocaine self-administration (PND 61-65), which included a cocktail of cocaine and histamine. Histamine was used to produce an aversive, delocalized itching sensation throughout the body that has previously been shown to act as an aversive stimulus. We hypothesized that rats exposed to non-contingent sucrose solution during the adolescent period would self-administer significantly greater number of infusions of cocaine/histamine compared to rats exposed to water. Sucrose treated adolescent male and female rats showed a trend to self-administer cocaine/histamine more so than the water exposed controls suggesting sucrose exposure produces increased resistance to punished cocaine in adulthood.

Disclosures: R. Parmar: None. M. Cobb: None. R. Arango: None. M. Wright: None. J. Parent: None. I.C. Sumaya: None. A.M. Gancarz: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.09/C32

Topic: A.09. Adolescent Development

Support: NIAAA grant p50AA017823-08
NIAAA grant U01AA019972-07
NIH grant T32 AA025606

Title: Adolescent male rats exhibit more persistent goal-directed behavior than do adults

Authors: *T. T. TOWNER¹, M. FAGER¹, L. P. SPEAR²

¹Psychology, Binghamton Univ., Binghamton, NY; ²Ctr. for Develop. and Behavioral Neurosci., Binghamton, NY

Abstract: Alcohol consumption is typically initiated during adolescence, with high levels of early alcohol increasing the probability for the later development of alcohol use disorders. In the transition from recreational use of alcohol to a more addictive-like consumption pattern, motivations for alcohol consumption may change from positive reinforcement to negative reinforcement. Along with this change in salience, development of problematic use patterns may be associated with a shift from goal-directed behavior to more habit-like behavior. Since adolescence is a period of greater vulnerability to alcohol consumption, it is possible that they are also at greater risk for the emergence of more habitual drinking than adults. In the current project, we hypothesized that adolescents would display greater evidence of habit-like responding after a random interval operant procedure in comparison to adults. The design used was a 2 age (adolescent; adult) x 2 schedule type (random ratio (RR); random interval (RI)) x 2 devaluation type (control; reinforcer) factorial. Adolescents were postnatal day (P)28 at the start of operant procedures whereas adults were P69. Animals were assigned to either the RR or RI training and underwent training on RR10 or RI30 for two days followed by four days of RR20 or RI60 training. After the last day of training, animals were given one hour free access to either home cage chow (control) or banana pellets (reinforcer) before undergoing an extinction trial. On the next day, animals were exposed to the opposite devaluation food and were again tested under extinction. When assessing rewards earned per minute during training, adolescent RR animals received more rewards than RI animals on days 6-10. Similarly, adults in the RR group received more rewards per minute on days 9 and 10. For the devaluation days, adolescents displayed less responding after reinforcer devaluation in comparison to adults, suggesting a more goal-oriented behavior rather than habit-like responding. In contrast to what we originally hypothesized, no differences were seen between RR and RI groups for either adolescents or adults. Overall, adolescent behavior was more goal-directed whereas adults appeared to have greater habit-like responding.

Disclosures: T.T. Towner: None. M. Fager: None. L.P. Spear: 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.; P50AA017823-08.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.10/C33

Topic: A.09. Adolescent Development

Support: MH102930
GM083883

Title: Age-dependent effects of EEDQ on cocaine-induced locomotor activity in male and female rats

Authors: A. TERAN, G. I. RAMIREZ, C. G. KATZ, *S. A. MCDOUGALL
Dept. of Psychology, California State Univ., San Bernardino, CA

Abstract: N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) is an alkylating agent that inactivates dopamine (DA) D2 receptors, as well as other receptor types, in preweanling, adolescent, and adult rats. Even so, the actions of EEDQ are not uniform across ontogeny. When compared to adolescent and adult rats, EEDQ preferentially leaves the surviving D2 receptors of preweanling rats in a high affinity state. In other words, even though EEDQ significantly reduces D2 receptor content in the dorsal striatum of preweanling rats, the remaining receptors are predominately of the D2^{High} variety. To determine whether these excess D2^{High} receptors have behavioral relevance, male and female preweanling, adolescent, and adult rats were given a single injection of vehicle or EEDQ (2.5 and 7.5 mg/kg, ip) on postnatal day (PD) 17, PD 39, or PD 84. On the test day, which occurred 24 h later, rats were injected with saline or cocaine (15 mg/kg, ip) immediately before being placed in locomotor activity chambers for 120 min. All rats, regardless of age, exhibited significantly elevated levels of locomotor activity after cocaine treatment. In adolescent and adult rats, EEDQ caused a dose-dependent reduction in cocaine-induced locomotor activity. This pattern of results is frequently reported and is caused by an EEDQ-induced inactivation of DA receptors. In striking contrast, EEDQ potentiated the locomotor activating effects of cocaine in male and female preweanling rats. This result is not unique, since a similar potentiation effect was observed when young rats were given an infusion of NPA (a direct D2 receptor agonist) into the dorsal striatum. When considered together, both sets of findings are consistent with the hypothesis that an EEDQ-induced increase in the percentage of high affinity D2 receptors is responsible for an exaggerated behavioral response in preweanling rats. The mechanism by which EEDQ produces a relative excess of D2^{High} receptors is uncertain; however, one possibility is that receptor repopulation occurs more rapidly during early ontogeny, and these newly synthesized receptors are predominately of the D2^{High} variety. In sum, DA receptor inactivation causes dramatically different behavioral effects across ontogeny: an outcome that may be due to age-dependent changes in the percentage of high-affinity D2 receptors.

Disclosures: A. Teran: None. G.I. Ramirez: None. C.G. Katz: None. S.A. McDougall: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.11/C34

Topic: A.09. Adolescent Development

Support: R01-MH086507
R01-MH105488

Title: Input-specific modulation of prefrontal afferent drive by $\alpha 7$ nAChR signaling *in vivo*

Authors: *A. M. MIGUELEZ FERNÁNDEZ, D. R. THOMASES, K. Y. TSENG
Dept. of Anat. & Cell Biol., Univ. of Illinois at Chicago - Col. of Med., Chicago, IL

Abstract: Abnormal elevation of the tryptophan metabolite kynurenic acid in the prefrontal cortex (PFC) is thought to contribute to the development of cognitive deficits in schizophrenia and related psychiatric syndromes. At the synaptic level, we have recently determined that increasing kynurenic acid levels in the PFC is sufficient to disrupt local processing of ventral hippocampal drive through an $\alpha 7$ nAChR-dependent mechanism. The aim of the present study is to further investigate the impact of $\alpha 7$ nAChR signaling in the regulation of PFC processing of afferent drive and determine to what extent such a modulation is input-specific. We found that PFC infusion of the $\alpha 7$ nAChR antagonist MLA markedly attenuated the potentiation of local field potential (LFP) responses elicited from the basolateral amygdala. However, this inhibitory effect of MLA was no longer apparent when delivered after the induction of LFP potentiation. Interestingly, PFC infusion of MLA did not disrupt the potentiation of LFP responses elicited from the ventral hippocampus. Instead, MLA markedly diminished the inhibitory component of the hippocampal drive such that a shift from LFP suppression to LFP facilitation emerges in the PFC. Accordingly, the normal inhibitory control of the amygdalar transmission in the PFC by the ventral hippocampus is also lost following prefrontal infusion of MLA. We then examined the behavioral impact of prefrontal $\alpha 7$ nAChR blockade and found that bilateral PFC infusion of MLA markedly disrupts the extinction of conditioned fear memory. Collectively, these results indicate that PFC $\alpha 7$ nAChR signaling differentially regulates hippocampal and amygdalar afferent information and their interactions in an input-specific manner. In this regard, any dysregulation of PFC $\alpha 7$ nAChR signaling is expected to trigger disruptions of PFC-dependent cognitive processes as seen in schizophrenia and related psychiatric disorders.

Disclosures: A.M. Miguelez Fernández: None. D.R. Thomases: None. K.Y. Tseng: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.12/C35

Topic: A.09. Adolescent Development

Support: MITACs
Canadian Institutes of Health Research

Title: Role of inflammatory signaling in pathophysiology of neuropsychiatric disorders induced by chronic adolescent THC exposure

Authors: *M. DE FELICE¹, J. RENARD¹, R. M. HUDSON¹, F. ZHOU GE¹, C. CHEN², L. WANG¹, S. N. WHITEHEAD¹, K. K. C. YEUNG², W. J. RUSHLOW^{1,3}, S. R. LAVIOLETTE^{1,3}
¹Dept. of Anat. and Cell Biology, Schulich Sch. of Med., ²Dept. of Chemistry, Dept. of Biochem., ³Dept. of Psychiatry, Univ. of Western Ontario, London, ON, Canada

Abstract: Marijuana is most commonly used during adolescence. Epidemiological studies have reported that adolescent marijuana exposure increases the risk of developing neuropsychiatric disorders (e.g. schizophrenia/depression) at adulthood.

Our group has previously demonstrated that chronic adolescent exposure to delta-9-tetrahydrocannabinol (THC) in rats, induces persistent neuropsychiatric-like symptoms and neuronal abnormalities, characterized by a dysregulation of cortical excitatory/inhibitory balance, GABAergic hypofunction and a potentiation of glutamatergic transmission in prefrontal cortex (PFC) (Renard et al 2017). Nevertheless, the mechanisms underlying the pathogenesis of these effects are still unclear.

Clinical evidence suggests that neuroinflammatory processes, involving microglial and astrocytic overactivation, have a key role in neuropsychiatric disorders. Dysregulation of the protein Glycogen Synthase Kinase 3 (GSK-3), expressed in both microglia and astrocytes, is also involved in inflammatory cytokine response and in psychiatric diseases. We have previously demonstrated that chronic adolescent THC exposure decreased PFC phosphorylated protein levels of GSK-3, which may result in both anti-inflammatory cytokines production and neuropsychiatric-like symptoms.

Hence, we hypothesized that adolescent THC exposure may increase inflammatory signaling, leading to the onset of pathological phenotypes.

Adolescent rats were treated during postnatal day (PND) 35-45 with increasing doses of THC (2.5mg/kg – 10mg/kg i.p., twice a day) or vehicle. At adulthood (PND 75), we used a Matrix-assisted laser desorption ionization Imaging Mass Spectrometry to investigate neuroanatomical distributions of cortical GABA and glutamate levels. Moreover, we examined potential inflammatory mechanisms using immunocytochemical analyses of microglial and astroglial activation markers. We have thus far found that chronic adolescent THC exposure induces an increase in cortical glutamate levels, consistent with a hyperactive state in PFC pyramidal neurons (Renard et al 2017). We are currently performing further analyses to quantify this change.

In addition, THC adolescent treatment strongly decreased PFC GSK-3 levels, which is associated with pro-inflammatory cytokine production. We are currently running OX-6 and GFAP immunostaining to analyze potential microglia and astrocyte activation patterns. Results from these studies will improve our knowledge of the neurobiological mechanisms implicated in the pathophysiology THC-induced neuropsychiatric symptoms resulting from neurodevelopmental exposure.

Disclosures: M. De Felice: None. J. Renard: None. R.M. Hudson: None. F. Zhou Ge: None. C. Chen: None. L. Wang: None. S.N. Whitehead: None. K.K.C. Yeung: None. W.J. Rushlow: None. S.R. Laviolette: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.13/C36

Topic: A.09. Adolescent Development

Support: NSERC

University of Ottawa

Title: Omega-3 supplementation during the adolescence period: Sex-specific effects on brain dha levels in juvenile and adult rats

Authors: *J. RAYMOND¹, H. PLAMONDON², M. SURETTE³

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³Univ. of Moncton, Moncton, NB, Canada

Abstract: INTRODUCTION: Food diversity and increased intake of un-synthesized molecules such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) is related to membrane formation and enhanced brain maturation. A diet rich in omega-3 (rich in DHA and EPA) has been linked to improved attention, cognitive performance and flexibility. Diet can also modify and/or improved brain plasticity during a vulnerable developmental period, such as the adolescence period. Elevated DHA and EPA concentrations in the hippocampus and prefrontal cortex tend to facilitate learning and memory throughout the adolescence and adulthood periods. The main goal of this study aimed to observe if a dietary change limited to the adolescence can influence DHA levels at a short (juveniles) and long-term (adulthood) in male and female rodents. METHODS: *Animals and conditions:* 24 post-weaning Wistar rats (n=12 males; n=12 females) were randomly assigned to one of the 4 different groups upon arrival. Control animals received soybean oil (C-SO) and the experimental groups received menhaden fish oil supplement (FO) daily. These groups received daily oil supplementation by oral gavage (0.3ml/100g body weight) during the early and mid-adolescence period (from PD28-47). Half of the experimental and control groups were sacrificed immediately following the gavage procedure while the other half were sacrifice during the adulthood period. *Tissue analysis:* Whole brain extraction was performed at age PND48 and PND90. Brain tissue was flash frozen in liquid nitrogen and stored at -80C until analysis. Fatty acid methyl esters, sterol esters, phospholipids, and triacylglycerols were extracted by gas-liquid chromatography using the FAMES procedure. RESULTS: the data has been collected and brain tissue is being analyzed. We expect that female will show increased DHA levels compare to males at both the juvenile and adult periods.

Disclosures: H. Plamondon: None. M. Surette: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.14/C37

Topic: A.09. Adolescent Development

Title: Adolescent high fat diet impairs motivation and disrupts prefrontal cortex gene expression in adulthood

Authors: *K. R. LLOYD, T. M. REYES

Psychiatry and Behavioral Neurosci., Univ. of Cincinnati, Cincinnati, OH

Abstract: In the human population, adolescent obesity is highly prevalent and is associated with deficits in prefrontal cortex (PFC)-dependent executive function. Adult bariatric surgery patients show improvements in executive function abilities after weight loss, with patients who were a healthy weight at age 18 showing a larger improvement than those who were obese at age 18, indicating that adolescent obesity has an enduring effect on the adult PFC. Because the PFC is still developing during adolescence, we investigated the effects of high fat diet (HFD) feeding on the development on the PFC in adolescent mice. Adolescent HFD exposure in rodents has been shown to cause deficits in working memory and reward-related behaviors, with some deficits persisting after removal of the HFD. We sought to extend these findings to PFC-dependent executive function behaviors, which have not been previously investigated in adult rodents following HFD exposure specifically in adolescence. We hypothesized that adolescent HFD exposure would impair adult executive function. C57Bl6/J x DBA F1 hybrid mice were fed either a 20% energy from fat control diet or a 60% energy from fat HFD during adolescence (either from 3-6 or 6-9 weeks of age) before all animals were switched to standard chow at 9 weeks of age. In adulthood, the mice were tested on touchscreen versions of the Fixed Ratio 1, Progressive Ratio, and 5 Choice Serial Reaction Time Task. Males showed decreased motivation specifically when the HFD was fed from 6-9 weeks of age, with simple rule-learning, impulsivity, and attention being unaffected by HFD. An additional group of behavior naïve mice were sacrificed at 15 weeks of age for gene expression analysis. In the PFC, adolescent HFD increased the expression of the genes coding for somatostatin and delta opioid receptor, while GABA transporter 1 was downregulated in the 6-9 week HFD exposure group. We conclude that adolescent HFD exposure disrupts gene expression in the PFC, with changes persisting even after bodyweight normalizes in adulthood.

Disclosures: K.R. Lloyd: None. T.M. Reyes: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.15/C38

Topic: A.09. Adolescent Development

Support: NSERC Discovery Grant 2NS

CFI 2NS

CRC2NS

NSERC Discovery RCPIN 341673

Title: Early-life exposure to DEHP results in acute hyperactive phenotype and increased astrocytic protein expression in males

Authors: *L. LAIRD, K. CHANDLER, C. A. RUDYK, M. R. HOLAHAN, N. SALMASO
Carleton Univ., Ottawa, ON, Canada

Abstract: Human exposure to environmental toxicants, such as phthalates, occurs throughout the lifespan. Phthalates are a group of synthetic chemicals added to plastics to increase their flexibility and durability, however they easily migrate out of the plastic product into the environment. Children and infants have a higher rate of exposure to phthalates than adults, which is concerning as the majority of neurodevelopment occurs during this time period. Previous research has shown that early life exposure to di-(2-ethylhexyl) phthalate (DEHP), the most commonly used phthalate worldwide, has resulted in altered dopaminergic innervation in the brain. Human research has suggested a correlation between early-life DEHP exposure and the onset of attention-deficit hyperactivity disorder (ADHD), a neurodevelopmental disorder. While the neuropathology of ADHD is not yet understood, suggested causes include altered dopaminergic function and abnormal prefrontal cortex (PFC) development. Because neurodevelopment includes many processes that are extensively mediated by astrocytes, it is hypothesized that DEHP exposure interferes with astrocytic functioning in such a way that results in disrupted dopaminergic innervation to the PFC, and results in a hyperactive phenotype. Using C57/Bl6 mice, DEHP was administered once daily from postnatal day (P) 18-23, a critical period of development of dopaminergic innervation to the PFC. Wildtype mice were used to assess behavioural changes. Transgenic AldH11-L10:GFP mice were used to measure changes in astrocyte number and astrocytic protein expression in the PFC using immunohistochemistry. Both behavioural and histological measurements were assessed at both P29 and P49, respectively, to examine both acute and chronic responses. Furthermore, we assessed both males and females to determine whether sex differences exist in response to early-life DEHP exposure. Our results suggest that male mice exposed to DEHP exhibit an acutely hyperactive phenotype, which is paralleled by increased expression of glial fibrillary acidic protein (GFAP). These

effects were not seen at P49, suggesting these effects are not long-lasting. No differences were seen at either time point between control females and females that received DEHP. These findings suggest that males and females differentially respond to early-life DEHP exposure, and further histological analysis will likely provide insight into how phthalate exposure can disrupt typical neurodevelopmental processes.

Disclosures: **L. Laird:** None. **K. Chandler:** None. **C.A. Rudyk:** None. **M.R. Holahan:** None. **N. Salmaso:** None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.16/D1

Topic: A.09. Adolescent Development

Support: NIH Grant P30 EY13079
NIH Grant R21MH105846
Fulbright Graduate Study Grant
F31 MH112372

Title: A causal role for the GABA_A receptor alpha 4 subunit in dorsal hippocampus in food restriction evoked wheel running

Authors: ***A. N. SANTIAGO**¹, A. SHERPA¹, Y.-W. CHEN², C. AOKI²
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Abstract: Despite the high mortality rate of anorexia nervosa, little is known about the neurobiological underpinnings of this disease. A rodent model, termed activity-based anorexia (ABA), allows us to examine the biological link between hyperactivity and reduced food consumption. Food restriction (FR) to 2 hrs per day evokes increased wheel running, which in turn precipitates rapid and potentially lethal weight loss as compared to FR without wheel access. Extent of FR-evoked running (FRER) correlates with FR-evoked increase in anxiety-like behavior (Wable et al 2015). Recent findings implicate deficits in GABAergic innervation of hippocampal CA1 in mice vulnerable to ABA. Moreover, an increase in extra-synaptic expression of the alpha4 subunit of the GABA_A receptor (alpha4GABA_AR) correlates with increased resilience to ABA in female, but not male mice. Here, we tested for the potential sex-specific causal link between alpha4-GABA_AR expression in dHPC and resilience to FR-stress as well as anxiety-like behavior by knocking down alpha4 subunits of GABA_ARs in dHPC. From mutant mice possessing loxP sites flanking exon 3 of the *Gabra4* gene (B6.129-Gabra4^{tm1.2Geh/J}; GABA_A-R alpha4^F, Jackson Lab strain 006874), we generated alpha4^F/alpha4^F homozygous (HOM; 6 females, 6 males) and alpha4⁺/alpha4⁺ (WT; 6 females, 4 males). At P24-26, they were

injected with AAV8-CMV-GFP-iCre (10^{13} GC/ml, 200 nl/hemisphere, Vector Biolabs) bilaterally into the dHPC. Wheel access (p36) was followed by 1st ABA (P41-P44), 7 days of recovery, 2nd wheel access, and 2nd ABA (P54-58), then euthanized (P58) to confirm viral transduction. FRER was measured as averaged wheel running during the 2nd and 3rd FR days of the 2nd ABA minus baseline running during the 2 days preceding FR. To allow adequate time for viral replication, reported analyses are for the second bout of ABA. FRER over the full 24hr cycle of ABA increased 3.6 fold in HOM vs WT females ($p=0.026$), but was not different across the genotypes in males. Likewise, HOM females ran 2.9 times the distance of WT females ($p=0.030$) specifically for the FRER during the 2 hrs of food allowance, indicating a voluntary choice to run vs eat. Unexpectedly, female HOM were less likely to exhibit food anticipatory activity (FAA-FRER) in the light-cycle hours preceding food allowance vs WT females ($p=0.060$), while HOM males were more likely to exhibit FAA-FRER vs WT males ($p=0.009$). These results indicate sex differences in hippocampal alpha4GABAa modulation across circuitries subserving FAA-FRER and 2hr-FRER.

Disclosures: A.N. Santiago: None. A. Sherpa: None. Y. Chen: None. C. Aoki: None.

Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.17/D2

Topic: A.09. Adolescent Development

Support: CONACYT 631998 (YMDLR)

Title: High-sucrose intake in post-weaned rats is associated with morphological and functional changes in rat testis

Authors: *Y. M. DE LEON RAMIREZ¹, P. PACHECO³, E. CUEVAS⁴, M. A. LARA GARCIA⁵, M. MARTINEZ-GOMEZ⁶, D. L. CORONA QUINTANILLA⁷, J. RODRIGUEZ ANTOLIN², L. NICOLAS TOLEDO²

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Abstract: Overweight is characterized by excessive storage of adipose tissue and high levels of triglycerides that contribute to vascular damage and trigger inflammatory response resulting in the adhesion of monocytes to endothelial cells leading to progressive arteriosclerosis. Diet rich in carbohydrates, induces endocrine disorders and metabolic syndrome. For example, leptin levels

increase with sucrose consumption in rats and are inversely correlated with testosterone levels. In contrast, the increase lactate levels favors the increase of testosterone which has been little studied in reproduction. Obese animals present a deterioration of sexual behavior associated with infertility. The pubococcygeus muscle, which participates in sexual function, has not been studied in the sugar water consumption model. In this respect, said muscle can change its metabolism, since it stores a large amount of testosterone-dependent glycogen. Thus, it is interesting to explore sugar water consumption effect at an early age on male sexual response through the urethrogenital (UG) reflex of Bsm and Pcm of male rats. We used male Wistar rats, 21 days-old divided into 2 experimental groups (8 / group): Control (C) and experimental (S30). All animals were maintained in individual cages with access to food Chow Purina 5001. According to the experimental group the rats belonged to tap water or 30 % sucrose solution for 30 days. Male rats were anesthetized and using a continuous saline solution injection through the urethra, penile urethral pressure as well as Bsm and Pcm electromyograms (EMGs) were recorded before, during and after urethrogenital reflex. Aliquots of blood were obtained to measure the concentration of leptin and testosterone by the Elisa method. Testis were removed and weighed for histological analysis, determine the expression of LDH and the number of sperm. Data were analyzed by a Student-t. The S30 animals showed an increase in testicular weight and diameter of the lumen with a decrease in the germinative epithelium, associated with an increase in leptin levels without affecting the testosterone concentration or triglyceride levels. In addition, they showed a higher expression of LDH in the tubular lumen, which correlates with the decrease in the number of sperm. Also, they have an altered Pcm and Bsm EMGs during this UG reflex, threshold pressure was increased and UG reflex duration and maximum pressure was decreased. Present study shows that a diet rich in sucrose at a young age has a greater impact on the testicular arrangement affecting both Bsm and Pcm response during UG reflex decreasing the number of sperm which may lead to male sexual dysfunction.

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Poster

033. Adolescent Development: Animal Models I

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.18/D3

Topic: A.09. Adolescent Development

Support: USEPA Grant RD-83543701
NIEHS Grant P01ES022831
NIEHS Supplement Grant P01ES022831-04S1

Title: Developmental nicotine exposure attenuates female sex behavior

Authors: *R. JOGLEKAR¹, M. CAULEY², H. WHITE, 27708², E. LEVIN², S. MURPHY³
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Abstract: Mammalian brain sexualization is developmentally mediated well after sex determination via gonadal hormones, and ultimately results in sexually dimorphic brain regions, both in structure and function. One such region, the preoptic area (POA), is responsible for adult sexual behavior and copulatory preference. Normal and induced masculinization of the POA was found to involve inhibition of DNA methylation and activation of methylation-dependent masculinizing genes (MDMGs) during postnatal days 0-4 in male and female rats. Tobacco use during pregnancy is common, and developmental nicotine exposure is known to impact DNA methylation. Further, a relationship between developmental nicotine exposure and altered sexual preference in exposed human females has been reported. Therefore, we hypothesized that developmental nicotine exposure would alter the methylation-dependent sexualization of the POA in rats. We used a rat model of gestational nicotine exposure via osmotic minipump (2mg/kg/day nicotine) from pre-mating through postnatal day 4 (PND4). PND2 POA was analyzed for MDMG expression using real-time PCR. Male sexual behavior (#mounts, #intromissions, #ejaculations, #anogenital sniffs) and female sexual behavior (#darts, #hops, #lordoses, #anogenital sniffs) were assessed at PND80. Using repeated measures analysis, we found an attenuation of female sexual behavior, including number of lordosis and darts/hops, in exposed vs controls (p=0.0074), but not in exposed or control males. We also found increased MDMG expression (p=0.0398) in nicotine-exposed male and female POA. Our results suggest that developmental nicotine exposure is capable of triggering the epigenetic masculinization of the rat POA.

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Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.19/D4

Topic: A.09. Adolescent Development

Support: Sigma Xi Grants in Aid of Research

Title: Paternal care influences oxytocin expression in male and female California mouse offspring and basal testosterone levels in female, but not male offspring

Authors: *A. GILL¹, A. LEITHEAD¹, C. YOHN², J. FORD¹, E. BECKER¹

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Abstract: Natural variations in parental behavior are associated with differences in expression of hormones, such as arginine vasopressin (AVP), oxytocin (OT), and testosterone (T), and have lasting effects on brain and behavior in offspring. Differences in parenting are, at least in part, programmed by the experience of paternal behavior during the postpartum period, as adult offspring model the degree of parental behavior they receive in development. Although paternal care in the biparental California mouse impacts future parental behavior in adult offspring, underlying mechanisms for this transmission are not fully understood. Transmission of territoriality in male and female offspring is mediated by transient increases in T following postnatal paternal retrievals and increased expression of AVP within the bed nucleus of the stria terminalis (BNST) in adulthood. It is unclear however whether OT, which is sensitive to gonadal steroids, is similarly impacted by father-offspring interactions. Using the California mouse, we manipulated levels of postnatal paternal care (high and low care) and examined differences in adult OT-ir expression within social brain areas. Additionally, to determine whether transient increases in T in response to postnatal paternal care results in long-term effects on development of the neuroendocrine system, we assessed basal plasma levels of T. Finally, we analyzed the relationship between OT-ir expression and T levels to determine if changes in the expression of these hormones were associated as OT expression is sensitive to gonadal hormones. . We found that high-care offspring had more OT-ir cells in the paraventricular nucleus (PVN), supraoptic nucleus (SON), and BNST, which have been implicated in the expression of behaviors such as aggression and parenting. Additionally, high-care females had higher levels of plasma T than low-care females, with no differences observed in males potentially due to a ceiling effect of T. Basal T levels were also positively associated with SON OT expression, suggesting that these hormones may mediate the development of social behavior. These data suggest future social behavior, like parenting, may be programmed by paternal care through lasting impacts on the neuroendocrine system.

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Poster

033. Adolescent Development: Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 033.20/D5

Topic: A.09. Adolescent Development

Title: Variation in early life maternal care predicts adolescent prefrontal cortex to amygdala synapse development in mice

Authors: *A. W. THOMAS¹, I. CHANG¹, K. DELEVICH¹, L. E. WILBRECHT²
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Abstract: During the adolescent transition from juvenile to adulthood, while prefrontal neocortex (PFC) dendritic spine density decreases and grey matter thins, the reciprocal projections between the basolateral amygdala (BLA) and prefrontal cortex undergo strikingly late growth. Late maturation of these circuits may subserve developmental behavioral changes and enable adaptation to the environment. To test if the development of BLA-PFC connectivity was sensitive to the early environment we used maternal separation (MS), three hours per day P1-10, as a rodent model of early life adversity, and quantified variation in maternal care in response to this manipulation. We then used a viral approach to label long range axons in the male offspring and quantified presynaptic boutons in postmortem brain slices during mid adolescence (P28-35). We focused on two frontal efferents projecting from the dorsomedial prefrontal cortex (dmPFC) to the basolateral amygdala (BLA) and dorsomedial striatum (DMS), and two frontal afferents whose axons emerge from cell bodies in the BLA and orbitofrontal cortex (OFC) and ramify in the same target region within dmPFC. We found MS treatment had specific effects on bouton density in the projection from the dmPFC to the BLA, but not other axons under study. The MS group had higher bouton density but smaller median dmPFC bouton size in the BLA at P35. The density of dmPFC boutons in the BLA also correlated with variation in maternal care across groups. Smaller, more numerous dmPFC boutons in the BLA could contribute to previously reported differences in cognitive flexibility in adolescence after MS treatment. Experience dependent scaling of PFC-BLA connectivity could reflect experience expectant adaptation to the environment, but may also contribute to greater risk for pathology.

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Poster

034. Neurotrophins

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 034.01/D6

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

Support: NICHD; ZIA-HD000711

Title: Analysis of neurodevelopment and schizophrenia-relevant behaviors in ErbB4 mutant mice lacking the Cyt-1 isoform

Authors: *L. M. ERBEN^{1,2}, M. E. CRONIN¹, M. SKIRZEWSKI¹, I. D. KARAVANOVA¹, D. VULLHORST¹, S. L. CARROLL³, A. L. BUONANNO¹

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Abstract: Genetic variants of Neuregulins (NRGs), and their cognate neuronal receptor ErbB4 have been associated with a risk for schizophrenia (Scz). Null ErbB4 knock-out (KO) mice exhibit imbalances in extracellular dopamine levels, neurodevelopmental impairments and behavioral deficits relevant to psychiatric disorders. ErbB4 transcripts are alternatively spliced at two locations: alternative splicing of JMa or JMb exons encoding the extracellular juxtamembrane region renders the receptor labile or resistant to metalloprotease-mediated cleavage, respectively. In the cytoplasmic domain, inclusion of the Cyt-1 exon 26 confers upon the receptor the ability to signal via the PI3K pathway, in contrast to Cyt-2 variants lacking exon 26. The ErbB4 Cyt-1 isoform comprises approximately 40% of ErbB4 in most brain areas, and independent studies have reported that ErbB4 transcripts including the Cyt-1 isoforms are increased in postmortem brains of Scz patients. To investigate the functional role of ErbB4 Cyt-1, we targeted exon 26 by site-directed recombination. Ablation of the Cyt-1 exon was confirmed by the absence of Cyt-1 transcripts in brain sections using a novel in situ hybridization approach that detects single-exon boundaries (BaseScope), and by quantitative real-time PCR using TaqMan probes. Importantly, absence of the Cyt-1 exon did not alter relative expression levels of Cyt-2 or JMa/JMb isoforms in mutant mice. We then investigated the extent phenotypes reported in ErbB4 KO mice are also present in Cyt-1 KOs. For example, GABAergic interneuron migration is altered in ErbB4 KO mice, resulting in reduced GABAergic interneurons in the adult cortex and hippocampus. We therefore investigated if lack of ErbB4 Cyt-1 expression alters interneuron migration and/or survival. Moreover, ErbB4 expressed in dopamine neurons has recently been shown to regulate extracellular dopamine levels, and ErbB4 KOs exhibit an imbalance of dopamine in several brain regions. We therefore analyzed extracellular dopamine levels in Cyt-1 KO mice by microdialysis. Lastly, we subjected Cyt-1 KO to a series of behavioral tests, as ErbB4 KO mice show behavioral deficits associated with psychiatric disorders, such as: hyperactivity, reduced anxiety, altered sensorimotor gating and impaired cognition. *This work was kindly supported by the Eunice Kennedy Shriver NICHD Intramural Research Program, NIH.*

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Poster

034. Neurotrophins

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 034.02/D7

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

Title: Erbb4 knock-out mice demonstrate behavioral deficits associated with extracellular dopamine disbalance in the brain

Authors: *M. E. CRONIN¹, M. SKIRZEWSKI², R. MURPHY², A. L. BUONANNO³
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Abstract: The ErbB4 tyrosine kinase receptor and its Neuregulin (NRG) ligands participate in a signaling pathway that is important for neuronal development and the regulation of excitatory/inhibitory balance in the brain. Genetic variants of *NRG1* and *NRG3*, and single-nucleotide polymorphisms and copy number of variants of ErbB4, have been repeatedly identified as genetic risk factors for the development of schizophrenia and its endophenotypes. ErbB4 is expressed in midbrain dopaminergic axons and inhibitory interneurons of the hippocampus and cortex. We and others have previously demonstrated that ErbB4 signaling regulates behaviors relevant to psychiatric disorders including hyperactivity, anxiety and cognitive-related behaviors, as well as basal steady-state extracellular dopamine levels in cortex, hippocampus and dorsal striatum (Skirzewski et al, 2017). To further investigate the role of ErbB4 in the modulation of dopamine signaling in the brain, as well as relevant behaviors, we used ErbB4-null mice (ErbB4-KO) in combination with *in vivo* microdialysis and behavioral testing relevant to dopamine function. Interestingly, our preliminary findings suggest that ErbB4-KO mice show region-specific dopamine deficits, compared to control animals. We found these deficits to be associated to previously unreported behavioral deficits that are dependent on dopamine function. Our progress thus far strongly suggests that ErbB4 signaling in dopaminergic mesolimbic and nigrostriatal systems is relevant to mechanisms of behaviors associated with psychiatric disorders. *This work was kindly supported by the Eunice Kennedy Shriver NICHD Intramural Research Program, NIH.*

The authors declare no financial conflicts.

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Poster

034. Neurotrophins

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 034.03/D8

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

Support: The Eunice Kennedy Shriver National Institute of Child Health and Human Development Intramural Research Program

Title: NMDA receptor-dependent shedding of NRG2 by matrix metalloproteinases

Authors: *D. VULLHORST¹, A. L. BUONANNO²

¹Section on Mol. Neurobio., NICHD, NIH, Bethesda, MD; ²Head of Cell Biol. Affinity Group, NICHD, Chief of Sect Mol Neurobiol (SMN), NICHD, NIH, Bethesda, MD

Abstract: Neuregulins (NRGs) are extracellular signaling factors whose membrane-bound proforms are proteolytically processed by extracellular proteases near their transmembrane domains to initiate signaling via ErbB receptor tyrosine kinases. Until recently, it was widely held that all NRGs target to axons where they regulate synapse formation and synaptic transmission via postsynaptic ErbB4 receptors expressed on GABAergic interneurons. However, we recently demonstrated in vitro and in vivo that NRG proforms with a single transmembrane domain (e.g., NRG2 and type II NRG1) are absent from axons and, instead, accumulate at neuronal subsurface cisterns (SSCs), a type of ER-PM junction, located on cell bodies and proximal dendrites. Shedding of the NRG ectodomain from these junctions is triggered by glutamate signaling via NMDA receptors and mediated by ADAM-type extracellular matrix metalloproteinases. These findings suggest that these NRGs at SSCs are involved in the homeostatic regulation of GABAergic interneuron excitability in response to increased excitatory transmission. However, how activity/glutamate regulates NRG ectodomain shedding from SSCs is currently not understood. We show here that NMDA receptor activation promotes ectodomain shedding in cultured neurons in two distinct yet converging ways – indirectly by promoting the dissociation of NRGs from ER-PM junctions, and directly by promoting ADAM shedding activity. Our findings reveal a novel functional relationship between NRGs, NMDA receptors and activity-dependent ectodomain shedding at SSCs. Taken together with earlier data from our group showing that NRG signaling via ErbB4 downregulates NMDA receptors (Vullhorst, Mitchell et al., Nat Comm 6:7222, 2015), these findings further support the notion of a close and reciprocal relationship between NRG/ErbB4 and NMDA receptor signaling pathways in GABAergic interneurons.

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Poster

034. Neurotrophins

Location: SDCC Halls B-H

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

Support: NIH 2014 RF1 AG

Title: Modulation of neuregulin 1 ectodomain shedding by glypican 4

Authors: *J. XU¹, B. DOMINGUEZ¹, F. DE WINTER², S. YEO¹, K.-F. LEE¹

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Abstract: Neuregulin1 (NRG1) is a leading schizophrenia susceptibility gene. NRG1 is a transmembrane protein that plays a pivotal role in neural development and synaptic plasticity. Following tightly regulated proteolytic cleavage of NRG1 transmembrane precursor protein (pro-NRG1), the NRG1 ectodomain binds and activates ErbB4 to elicit signaling cascades. But the molecular mechanisms underlying the regulated cleavage and shedding of NRG1 ectodomain are not well understood. A proteomics approach reveals that glypican 4 (Gpc4), a cell surface heparan sulfate proteoglycan containing a core protein anchored to the cytoplasmic membrane via a glycosyl phosphatidylinositol (GPI) linkage, is one of NRG1 interactors. Here we show that Gpc4 is a strong stimulator of NRG1 ectodomain cleavage and shedding. Gpc4 stimulates NRG1 cleavage and secretion in HEK 293 cells in trans via an GPI-dependent and glycosylation-dependent mechanism. Similarly, in mouse primary neuron cultures, lentiviral overexpression of Gpc4 in astrocytes augmented secretion of virally expressed NRG1 by mouse cortical neurons, whereas lentiviral overexpression of Gpc4 in cortical neurons enhanced secretion of NRG1 expressed by virally transduced astrocytes, in an GPI- and glycosylation-dependent manner. On the contrary, when Gpc4 was overexpressed in cis with pro-NRG1, NRG1 cleavage and secretion was not affected. Homodimerization of pro-NRG1 monomers represents an essential pre-condition for its regulated ectodomain cleavage. NRG1 homodimerization was enhanced by Gpc4 over-expressed in trans in both HEK293 cells and primary mouse cortical neurons. Primary cortical neuron cultures prepared from Gpc4 null fetus showed decreased cleavage and secretion of NRG1 exogenously expressed by transduced cortical neurons compared with those from wild type fetus. Consistently, NRG1 cleavage was diminished in the brains of Gpc4 null mice. Interestingly, these Gpc4 null mice exhibited impaired pre-pulse inhibition behavior, indicative of schizophrenia-like deficits. Together these results identify a novel interaction between NRG1 and Gpc4 whereby Gpc4 modulates NRG1 cleavage and shedding.

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Poster

034. Neurotrophins

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

Support: R01MH097803 awarded to AG
R21MH113154 awarded to AG

Title: EGR3 is required for activity dependent Bdnf exon IV and VI induction in the mouse hippocampus

Authors: *K. K. MARBALLI¹, X. ZHAO², K. T. MEYERS^{1,3}, J. M. CAMPBELL¹, A. L. GALLITANO¹

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Abstract: Early growth response 3 (*Egr3*) is an immediate early gene transcription factor (IEG TF) that we have previously reported to be essential for hippocampal long term depression (LTD) and spatial memory. However, the molecular mechanisms by which *Egr3* influences these processes remain unknown. To identify activity-dependent transcriptional targets of EGR3 in the hippocampus, we conducted an expression microarray in both wildtype (WT) and *Egr3*^{-/-} mice following electroconvulsive stimulation (ECS), a potent inducer of IEGs. Of the differentially expressed genes identified, brain derive neurotrophic factor (*Bdnf*) stood out as the sole growth factor. Quantitative real time PCR (qRT-PCR) showed that *Bdnf* was upregulated in WT mice after ECS, consistent with prior reports that hippocampal *Bdnf* is upregulated by seizure. However, this induction was absent in *Egr3*^{-/-} mice. We validated these data in two independent cohorts using qRT-PCR. BDNF is a multifunctional protein in the nervous system, an important player in hippocampal LTD, and a known upstream regulator of *Egr3*. Based on our data we hypothesized that *Egr3* regulates activity-dependent induction of *Bdnf* in the hippocampus. We focused our studies on *Bdnf* exons IV and VI, two activity dependent exons that are highly expressed in the hippocampus. Using the same three cohorts from our previous study, we assayed levels of transcripts containing *Bdnf* exons IV and VI, using qRT PCR. *Bdnf* exon IV and VI mRNAs were each highly induced by ECS in WT mice, but not in *Egr3*^{-/-} mice, across all cohorts. Follow-up *in vitro* luciferase reporter studies showed that *Egr3* overexpression in mouse neuro2a cells activates *Bdnf* -promoter driven exon IV and VI containing transcripts. These data demonstrate that *Egr3* is necessary for induction of exon IV and, to a lesser extent, of exon VI *Bdnf* transcripts, in the mouse hippocampus following ECS. Our findings suggest the possibility that *Egr3* may regulate activity-dependent *Bdnf* expression following physiologic stimuli, such as those that influence learning and memory. Our results identify EGR3 as a novel transcriptional regulator of activity-dependent hippocampal *Bdnf* expression.

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Poster

034. Neurotrophins

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

Support: Grant # 14182MFDS977
NRF-2016R1A2B1010564
NRF-2018R1A2B6003000

Title: Nicotine challenge regulates BDNF via stimulation of metabotropic glutamate receptor 5-coupled signaling cascades in the dorsal striatum

Authors: ***J. KIM**¹, J. YANG², S. SON³, S. KIM³, E. HAN³, E. CHOE³

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Abstract: Brain-derived neurotrophic factor (BDNF) is a member of neurotrophic family, which functions in the regulation of synaptic plasticity in the brain. Exposure to drugs of abuse increases glutamate releases and BDNF expression followed by a variety of signaling cascades coupled to TrkB, which contributes to the control of glutamatergic homeostasis. Our preliminary study demonstrated that intra-caudate infusion of mGluR5 antagonist, MPEP (0.5 nmol), significantly decreased nicotine challenge (1.0 mg/kg, s.c.)-induced increase in BDNF expression in the dorsal striatum (CPu). Triple-immunofluorescent analysis showed that the increased number of BDNF and NeuN double labeled cells, as well as GAD67 double labeled cells after nicotine challenge injections significantly decreased by intra-caudate infusion of MPEP in the dorsal striatum. It suggests that the role of BDNF in the regulation of mGluR5 mediated-glutamatergic transmission in response to nicotine challenge exposure through the CPu, a key structure in the basal ganglia circuitry of basal forebrain. It would be expected that GABAergic neurons in the dorsal striatum have benefit to control the antero- or retrograde releases of BDNF. Based on this speculation, we will determine potential mechanisms underlying the nicotine challenge-induced BDNF releases by investigating the following hypothesis. Increases in the releases of glutamate after nicotine challenge administration regulate BDNF via stimulation of mGluR5-coupled signaling cascades in the dorsal striatum.

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Keyword: Ca²⁺ cascade, glutamate, neurotrophic factor, psychostimulant, tobacco

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Poster

034. Neurotrophins

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Program #/Poster #: 034.07/D12

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

Support: Joint Brazilian-Swedish Research Collaboration STINT-CAPES Grant
Thurings Foundation Grant
Gållöstiftelsen

Title: Altered BDNF-trkB signaling in parvalbumin interneurons in the prefrontal cortex induces changed oscillatory activity and behavior

Authors: *N. G. GUYON¹, C. LOPES-AGUIAR³, L. R. ZACHARIAS⁴, M. Y. ZILBERTER⁵, Y. XUAN¹, H. KIM¹, J. IMMENSCHUH¹, R. H. ANDERSSON², M. LINDSKOG², A. FISAHN², K. MELETIS¹, M. CARLÉN¹

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Abstract: Cortical inhibitory interneurons expressing parvalbumin (PV) have a vital role in modulating cortical output and plasticity. Synaptic inhibition provided by PV interneurons regulates neuronal excitability, and is also involved in the generation of gamma oscillation. Cortical gamma oscillations are correlated to cognition, and dysfunction of PV neurons in the prefrontal cortex (PFC) is implicated in the pathophysiology of a range of neuropsychiatric disorders characterized by changed cognition.

Altered *brain-derived neurotrophic factor* (BDNF) - *tyrosine receptor kinase B* (trkB) signaling involving cortical PV neurons have been associated with pathophysiology in schizophrenia. Increased expression of truncated trkB isoforms, unable to mediate normal neurotrophic responses, have been demonstrated in PV neurons in individuals affected by schizophrenia. The changed expression is correlated with altered GABA inhibition in humans and altered local network synchronization in mice.

To directly investigate the functional role of BDNF-trkB signaling in PV interneurons in the PFC, we generated an adeno-associated virus (AAV) with Cre-dependent expression of a dominant negative trkB receptor (trkB.DN; a truncated receptor that binds to BDNF but does not trigger intracellular signaling cascades). Expression of TrkB.DN in PV neurons in the medial PFC (mPFC) induced aggressiveness and disturbances in behavior related to memory, fear and anxiety, but did not affect general locomotion. *In vivo* electrophysiological recordings in freely moving animals revealed changed oscillatory activity in the mPFC, primarily affecting the gamma band, findings corroborated with recordings under urethane anesthesia. *In vitro* slice electrophysiology demonstrated unaltered membrane properties and action potential spike shape in prefrontal PV neurons expressing trkB.DN, but also a lowered level of inhibitory activity and increased excitation in the local circuit.

We hope that our study will elucidate how changes in BDNF-trkB signaling involving prefrontal PV interneurons relate to behavioral alterations and prefrontal hyperactivity in neuropsychiatric disorders.

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Poster

034. Neurotrophins

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 034.08/D13

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

Support: Estonian Research Council (institutional research funding IUT19-18)
European Union through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012)

Title: CREB and BDNF transcriptional autoregulation

Authors: *E.-E. ESVALD, J. TUVIKENE, A. SIRP, T. TIMMUSK
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Abstract: Brain-derived neurotrophic factor (BDNF) is a potent neurotrophin influencing the differentiation and survival of neurons in the developing central nervous system. In the adult nervous system BDNF also supports the formation of synapses and synaptic plasticity. It has been described that BDNF signaling via its receptor TrkB induces the expression of BDNF gene and forms a transcriptional autoregulative loop in cortical neurons. We have previously described the involvement of AP-1 transcription factors in the autoregulation of BDNF promoter I in cortical neurons, but the molecular mechanism responsible for the TrkB signaling-dependent activation of other BDNF promoters has not been described in detail. Here we have investigated the transcriptional regulation of BDNF gene by BDNF-TrkB signaling in rat primary cortical neurons using overexpression of dominant-negative CREB, gene silencing with CRISPR interference, promoter analysis by luciferase reporter assay and chromatin immunoprecipitation analysis. Our results elucidate the mechanism of BDNF gene regulation and clarifies the role of CREB family transcription factors.

Disclosures: E. Esvald: None. J. Tuvikene: None. A. Sirp: None. T. Timmusk: None.

Poster

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

Support: ERC grant No 322742-iPLASTICITY
Sigrid Jusélius foundation
Brain&Mind doctoral programme

Title: Ketamine and (2R,6R)-hydroxynorketamine induce ocular dominance plasticity in the adult mouse visual cortex

Authors: *A. STEINZEIG¹, H. ANTILA¹, C. CANAROZZO¹, T. D. GOULD², E. CASTRÉN¹
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Abstract: Neuronal plasticity is known to be prominent during critical periods in early development but more restricted in adult brain. However, recent studies showed that chronic administration of the antidepressant fluoxetine reinstates a juvenile-like form of plasticity in the adult rodent visual cortex. We hypothesize that the cellular mechanisms underlying these actions—though operating within distinct circuits—are relevant to the mechanism of antidepressant actions. The neurotrophic factor BDNF and its receptor TrkB were shown to play a key role in this induced plasticity. Whether other antidepressant drugs are able to restore ocular dominance plasticity and what is the mechanism of their action remains unknown.

Ketamine is an NMDA receptor antagonist that has rapid-acting antidepressant actions in both clinical and animal studies. Ketamine is rapidly metabolized to norketamine, dehydronorketamine and a number of hydroxynorketamines (HNKs) that have distinct biological activities. (2S,6S) and (2R,6R)-HNK are the most abundant HNK metabolites found in mouse brain and plasma. Previous research (Zanos et al., 2016) demonstrated antidepressant effect of (2R,6R)-HNK independent of ketamine and NMDA receptor inhibition.

In the current study we investigated effect of ketamine and (2R,6R)-HNK on ocular dominance (OD) plasticity after 7 days of monocular deprivation in the adult mouse visual cortex using the intrinsic signal optical imaging method. Ketamine or (2R,6R)-HNK were administered (10 mg/kg) at the onset of and every third day during 7 days of monocular deprivation. Our results demonstrated the robust ability of (2R,6R)-HNK to reinstate OD plasticity in adult mouse visual cortex that is comparable to that observed after chronic fluoxetine treatment, while at the same dose ketamine produced a small but significant effect.

The ability of the antidepressants to enhance neuronal plasticity in the brain is considered to be one of possible mechanism of antidepressant action. Establishing the mechanisms of this adult

brain plasticity and the role of BDNF/TrkB signaling has practical significance for refinement of antidepressant therapy in humans. Our findings in the OD model have relevance to synaptic actions of (2R,6R)-HNK within other affect-regulating synapses.

Disclosures: A. Steinzeig: None. H. Antila: None. C. Canarozzo: None. T.D. Gould: None. E. Castrén: None.

Poster

034. Neurotrophins

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

Support: Estonian Research Council (institutional research funding IUT19-18)
European Union through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012)

Title: Identification of enhancer regions regulating BDNF gene expression

Authors: *J. TUVIKENE, A. AVARLAID, K. UUSTALU, A. RÄHNI, E.-E. ESVALD, K. JAANSON, T. TIMMUSK

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Abstract: Brain-derived neurotrophic factor (BDNF) controls the survival, growth and function of neurons both during the development and in the adult nervous system. The expression of BDNF is induced in response to various stimuli, including neuronal activity and TrkB signalling. However, while the proximal *cis*-regulatory elements necessary for the regulation of the BDNF gene expression have been well characterized, little is known about the distal regulatory elements of the BDNF gene. Here, we have used bioinformatic prediction to identify putative enhancer regions responsible for the regulation of BDNF gene expression. To interrogate the functionality of these putative enhancer regions in rat primary neural cells, we used luciferase reporter analysis, lentivirus-mediated CRISPR interference and CRISPR activator systems, and chromatin immunoprecipitation analysis. Collectively, we have identified two novel potential enhancer regions participating in the regulation of the BDNF gene expression in rat primary neurons.

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Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

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Program #/Poster #: 035.01/D16

Topic: B.04. Ion Channels

Support: FWO fellowship 12U7918N
FWO grant V401218N
CIHR grant FDN-154286

Title: The role of TRPM3 in the hippocampus

Authors: ***K. HELD**^{1,2}, T. VOETS², Y. WANG¹, J. VRIENS²

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Abstract: TRPM3 belongs to the superfamily of transient receptor potential (TRP) channels and forms a non-selective cation conducting ion channel that has been shown to play a pivotal role in the sensory nervous system. It is expressed in trigeminal and dorsal root ganglia neurons, where it is involved in pain sensation and inflammatory hyperalgesia. Like most TRP channels, it is a polymodally-activated ion channel that is responsive to several different stimuli. Despite intensive investigations within the last few years, TRPM3 remains as a not well-characterized ion channel. For instance, expression of TRPM3 is indicated in several other tissues outside of the peripheral nervous system, while the functional roles of TRPM3 in these tissues still have to be established. Several groups had reported the abundant expression of TRPM3 in the brain, including the hippocampus. Interestingly, the neurosteroid and endogenous TRPM3 agonist pregnenolone sulfate (PS) was reported to have influences on synaptic transmission and long-term potentiation (LTP). Additionally, a recent study reported antagonistic effects of the anti-epileptic drug primidone on TRPM3, proposing a potential role of TRPM3 in disease conditions of the brain. Therefore, we propose that TRPM3 may play a functional role in the brain and more specifically in the hippocampus. In this study, we explore the role of TRPM3 in the hippocampus by a combined approach of electrophysiology and molecular biology. First, we will investigate TRPM3 expression in the hippocampus by use of RNAscope. Second, we will test TRPM3 agonists and antagonists on hippocampal cell cultures and monitor the effects by use of the whole-cell patch clamp technique. Finally, we will perform field potential and whole-cell patch clamp recordings in CA1 of mice hippocampal slices to determine the role of TRPM3 in LTP/LTD and synaptic plasticity. All measurements on brain slices will be performed in male C57BL/6 mice between 2-6 weeks of age. TRPM3-deficient mice will be used as negative controls. Our study will provide novel insights in the (patho)physiological functions of TRPM3 within the central nervous system.

Disclosures: **K. Held:** None. **T. Voets:** None. **Y. Wang:** None. **J. Vriens:** None.

Poster

035. Sensory Transduction and Other Ion Channels

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Program #/Poster #: 035.02/D17

Topic: B.04. Ion Channels

Support: FONDECYT 11140731
FONDECYT 1181814

Title: TRPM4 modulates excitability of pyramidal neurons at layer 2/3 mPFC

Authors: *E. LEIVA-SALCEDO, D. RIQUELME
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Abstract: TRPM4 is a Ca²⁺-activated non-selective cation (CAN) channel that conducts monovalent cations. This channel regulates the membrane potential in a Ca²⁺-dependent way in both excitable and non-excitable cells. We recently demonstrated that TRPM4 is localized in the soma and in the proximal dendrite while absent in the axon initial segment. In addition, TRPM4 current is active at resting membrane potential. Here we use a combination of whole-cell patch-clamp, nystatin-perforated patch-clamp and multiplex immunofluorescence labeling to characterize the function and expression of TRPM4 in the mouse medial prefrontal cortex (mPFC) layer 2/3. We found that TRPM4 activation depolarizes membrane potential. Moreover, we found that TRPM4 inhibition using 9-Phenanthrol increases membrane resistance and reduces rheobase. After synaptic stimulation using a high frequency stimulation (HFS), we found that TRPM4 inhibition reduces firing frequency and decreases EPSP slope in pyramidal neurons. Additionally, the silencing of TRPM4 in pyramidal neurons (shRNA) obliterates the increase in firing frequency induced by HFS and renders neurons insensitive to 9-Ph. Together, these results confirm that TRPM4 is active at resting membrane potential, and after HFS, its inhibition reduce the excitability of the neurons, suggesting a role of TRPM4 in the modulation of the neuronal excitability.

Disclosures: E. Leiva-Salcedo: None. D. Riquelme: None.

Poster

035. Sensory Transduction and Other Ion Channels

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 035.03/D18

Topic: B.04. Ion Channels

Support: NIH Grant NS064135

Title: Expression of TRPV1 channels by Cajal-Retzius cells and layer-specific modulation of synaptic transmission in the mouse hippocampus

Authors: M. ANSTÖTZ, S. LEE, *G. MACCAFERRI
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Abstract: The vanilloid receptor TRPV1 forms complex polymodal channels that are expressed by sensory neurons and play a critical role in nociception. Their distribution pattern and functions in cortical circuits are, however, much less understood. Although TRPV1 reporter mice have suggested that, in the hippocampus, TRPV1 is predominantly expressed by Cajal-Retzius cells (CRs), direct functional evidence is missing. As CRs powerfully excite GABAergic interneurons of the molecular layers, TRPV1 could play important roles in the regulation of layer-specific processing. Here, we have taken advantage of calcium imaging with the genetically-encoded indicator GCaMP6s and patch-clamp techniques to study the responses of hippocampal CRs to the activation of TRPV1 by capsaicin, and have compared the effect of TRPV1 stimulation on synaptic transmission in layers innervated or non-innervated by CRs. Capsaicin induced both calcium responses and membrane currents in ~50% of the cell tested. Neither increases of intracellular calcium nor whole-cell currents were observed in the presence of the TRPV1 antagonists capsazepine/ruthenium red or in slices prepared from TRPV1 knockout mice. We also report a powerful TRPV1-dependent enhancement of spontaneous synaptic transmission onto interneurons with dendritic trees confined to the layers innervated by CRs. In conclusion, our work establishes that functional TRPV1 is expressed by a significant fraction of CRs and we propose that TRPV1 activity may regulate layer-specific synaptic transmission in the hippocampus. Lastly, as CR density decreases during postnatal development, we also propose that functional TRPV1 receptors may be related to mechanisms involved in CR progressive reduction by calcium-dependent toxicity/apoptosis.

Disclosures: M. Anstötz: None. S. Lee: None. G. Maccaferri: None.

Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 035.04/D19

Topic: B.04. Ion Channels

Title: Discovery of novel co-activators of trpv1 and trpa1 to promote chemical neurostimulation for the treatment of muscle cramps and spasms

Authors: ***G. SHORT**¹, **A. BROCKMAN**², **R. PERNI**², **W. MCVICAR**³

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Abstract: Chemical neurostimulation is a general method to treat neurological conditions by stimulating sensory neurons with small molecules to alter the behavior of distinct neural circuits within the central nervous system. FLX-787, currently under clinical development, is a co-activator of TRPV1 and TRPA1 and is thought to stimulate sensory fibers in the oropharynx and esophagus to promote activation of brainstem nuclei that trigger monoaminergic release in the spinal cord. Monoaminergic excitation of inhibitory interneurons in the dorsal horn is believed to reduce the hyperexcitability of the alpha motor circuitry to decrease the frequency of muscle cramps and spasms. FLX-787 treatment has demonstrated efficacy in several recently reported clinical studies, significantly reducing muscle cramps, spasms and associated pain in patients with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) with clinically meaningful benefit.

To identify additional coactivators of TRPV1 and TRPA1, a focused screening and structure-activity relationship effort was undertaken. Over one hundred known and novel chemical entities (NCEs) were screened using fluorescent imaging of cell lines expressing either human TRPV1 or TRPA1. Two lead NCE's based on a capsaicin scaffold were identified that enabled coactivation of both ion channels at similar potencies. Capsaicin typically displays selectivity for TRPV1. However, through iterative cycles of medicinal chemistry refinement, TRPA1 activity was engineered successfully into the capsaicin scaffold. The two NCEs, demonstrated improved potency over FLX-787. On-going behavioral studies are assessing the degree of aversion upon oral administration and activation of TRPV1 and TRPA1 in rats.

These data demonstrate that a novel class of TRPV1 and TRPA1 coactivators has been identified and may likely serve as chemical neurostimulators to inhibit alpha motor neuron hyperexcitability as FLX-787 albeit with improved potency. These second-generation molecules may provide enhanced efficacy and broad applicability in the treatment of muscle cramps, spasms and associated symptoms in neurological disease.

Disclosures: **G. Short:** A. Employment/Salary (full or part-time); Flex Pharma. **A. Brockman:** 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.; Flex Pharma. **R. Perni:** 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.; Flex Pharma. **W. McVicar:** A. Employment/Salary (full or part-time); Flex Pharma.

Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

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Program #/Poster #: 035.05/D20

Topic: B.04. Ion Channels

Support: R01NS092645-01A1

Title: Characterization and optimization of the novel TRPM2 antagonist tat-M2NX

Authors: *I. CRUZ-TORRES¹, P. S. HERSON²

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Abstract: Introduction: We and others have identified TRPM2, a non-selective cation channels highly expressed in the brain, as a contributor to neuronal injury caused by stroke or cardiac arrest. However, the lack of specific inhibitors hinders the study of TRPM2 in pathophysiology. Our lab designed tat-M2NX to prevent ligand binding and TRPM2 activation. Tat-M2NX reduces ischemic injury in wild-type male mice. The lack of effect of tat-M2NX treatment in TRPM2 knockout mice provides evidence of specificity. In the current study, we performed mutagenesis of tat-M2NX to determine potency, binding affinity, and antagonistic mechanism.

Materials and Methods: We assessed tat-M2NX antagonism by heterologous expression of human TRPM2 channels in HEK-293 cells. To determine potency, whole-cell patch clamp recordings were performed in the presence of 100 μ M ADPR (agonist) and 0, 0.05, 0.15, 0.3, 0.5, 2, 5, and 10 μ M tat-M2NX in the pipette. TRPM2 currents were quantified using maximal peak amplitude in the absence and presence of tat-M2NX, followed by bath application of the pore blocker clotrimazole. Binding interaction of tat-M2NX to TRPM2 was tested with co-immunoprecipitation. Tat-M2NX mutant and truncated peptides were tested (2 μ M): scramble, single point mutations, and truncations. All experiments had access resistance of $R_a < 15 \text{ M}\Omega$ in addition to a final leak current $< 350 \text{ pA}$. Current density (pA/pF) was analyzed for each experiment. Potency, or IC_{50} , was calculated from $\log [\text{tat-M2NX}]$ vs normalized response curve. Statistical significance was established as $p < 0.05$ for all groups using *t*-test or One-Way Analysis of Variance. **Results and conclusions:** Tat-M2NX inhibits $> 90\%$ of TRPM2 channel currents at concentrations 0.5, 2, 5, and 10 μ M suggesting that tat-M2NX is an effective TRPM2 antagonist. Moreover, tat-M2NX is a potent antagonist with an IC_{50} of approximately 214nM. Our results from tat-M2NX mutagenesis experiments indicate that specific residues within the tat-M2NX C-terminus are required to confer antagonism on TRPM2. Therefore, the peptide tat-M2NX represents a new tool for the study of TRPM2 function in cell biology to enhance our understanding of neurological diseases and stroke.

Disclosures: I. Cruz-Torres: None. P.S. Herson: None.

Poster

035. Sensory Transduction and Other Ion Channels

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Topic: B.04. Ion Channels

Support: Ministry of Science, ICT (information & Communication Technology) and Future Planning (MSIP) Grant 2015R1A2A1A05001756 to I.S
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Title: Regulation of transient receptor potential canonical (TRPC)4, TRPC5 homomeric and TRPC1/4, C1/5 heteromeric channel activities by PI(4,5)₂ hydrolysis

Authors: *J. KO¹, J. MYEONG^{1,2}, Y. SHIN³, I. SO¹

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Abstract: Transient receptor potential canonical (TRPC) 4 and TRPC5 are known to be modulated by the G α_q -PLC pathway. Since phosphatidylinositol 4,5-bisphosphate (PI(4,5)P₂) maintains TRPC4 and TRPC5 channel function, the G α_q -PLC pathway inhibits channel activity by hydrolyzing PI(4,5)P₂. Here we investigated the difference in PI(4,5)P₂ sensitivity between homomeric and heteromeric TRPC channels. First, by using a *Danio rerio* voltage-sensing phosphatase (Dr-VSP), we show that PI(4,5)P₂ dephosphorylation robustly inhibits not only TRPC4 α , TRPC4 β , and TRPC5 homotetramer currents but also TRPC1/C4 α , TRPC1/C4 β , and TRPC1/C5 heterotetramer currents. Secondly, the sensitivity of homotetramers to PI(4,5)P₂ dephosphorylation increased in the sequence TRPC4 β < TRPC4 α < TRPC5, whereas when forming heterotetramers with TRPC1, the sensitivity was approximately equal between the channels. Thirdly, we determined putative PI(4,5)P₂ binding sites based on a TRPC4 prediction model. By neutralization of basic residues, we identified putative PI(4,5)P₂ binding sites both because the mutations reduced FRET to a PI(4,5)P₂ sensor and reduced the current amplitude. Therefore, one functional TRPC4 has 8 pockets with the two main binding regions; K419, K664 / R511, K518, H630. We conclude that PI(4,5)P₂ is required for TRPC1/4 and C1/5 heterotetramer activities as well as TRPC4, C5 homotetramers with different sensitivities.

Disclosures: J. Ko: None. J. Myeong: None. Y. Shin: None. I. So: None.

Poster

035. Sensory Transduction and Other Ion Channels

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Topic: B.04. Ion Channels

Support: NRF-2015R1A2A1A05001756
BK PLUS of NRF

Title: Polyamine-mediated inward rectification of TRPC4 channel

Authors: *Y. BAIK, J. KIM, I. SO

Dept. of Physiol., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Transient Receptor Potential Canonical 4 (TRPC4) channel is a Ca^{2+} -permeable, non-selective cation channel. TRPC4 is expressed in various tissues such as brain, thyroid, ventricular myocyte, kidney, uterus, gonads, lung and lower GI tracts. Although exact physiological role of the channel at those tissues are still remaining unknown, it has been reported that TRPC4 is essential for ileal smooth muscle contraction stimulated by parasympathetic nervous system. With its inward-rectifying I-V relationship and high Ca^{2+} permeability, TRPC4 channels permit Ca^{2+} influx once the channel is opened by muscarinic receptor stimulation by acetylcholine or by carbachol, a potent acetylcholine homologue. Molecular mechanistic study for the nature of inward rectification has been conducted in inward-rectifying potassium channels ($\text{Kir}_{2.1}$) with Mg^{2+} and polyamines being putative rectification mediators. Meanwhile, we reported that intracellular spermine blocks TRPC4 channel through electrostatic interaction with two glutamate residues. Here, with electrophysiological analysis and structural modelling, we suggest that there are two-different spermine binding sites (shallow site and deep site) in TRPC4 channels. These sites were different from each other in view of voltage-dependency and time-dependency. While time constant for spermine-mediated blocking showed saturation at highly depolarized voltage (over +40 mV) in $\text{Kir}_{2.1}$, blocking time constant for TRPC4 showed no saturation. This difference may be correlated with critical difference in I-V relationship of two channels at highly depolarized voltage; $\text{Kir}_{2.1}$ does not show outward current burst but TRPC4 does.

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Poster

035. Sensory Transduction and Other Ion Channels

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Topic: B.04. Ion Channels

Support: NSF 1535790

Title: Temperature sensitivity of GR28bD and its orthologs in *Drosophila*

Authors: *A. MISHRA, A. ROBINSON, B. R. BERIGAN, M. AMIRSHENAVA, J. L. LIN, B. C. ZARS, M. MILESCU, L. MILESCU, T. ZARS
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Abstract: Extrinsic control of neuronal activity is necessary to understand the neural processes underlying behaviour. Tools based on modalities like light and temperature are used to influence neuronal activity. Thermogenetics, which relies on activation of temperature sensitive proteins to manipulate neuronal activity is limited by the highly conserved and commonly used Transient Receptor Potential Channel proteins. We recently showed that the temperature sensitive gustatory receptor GR28bD in *D. melanogaster* can be used as a thermogenetic tool. In order to increase the repertoire of thermogenetic tools, we tested the temperature response properties of orthologs of GR28bD from 5 other *Drosophila* species that had 80-98% sequence identity to GR28bD. To determine if the orthologs are temperature sensitive, we overexpressed them pan-neuronally with *nSyb-Gal4* and assayed for temperature dependent paralysis of flies in the heat-box. Briefly, the flies were subjected to temperatures of 24-40°C in steps of 2°C in the heat box, a high throughput machine with a resolution of 1°C. They were exposed to each temperature step for 90s. Our results showed that the majority of flies overexpressing orthologs from *D. simulans*, *D. yakuba*, or *D. pseudoobscura*, which are 98, 96, and 85% identical to GR28bD were paralyzed between 30 and 32°C. Flies with mis-expression of *D. willistoni* ortholog, which is 81% identical to GR28bD were paralyzed between 36 and 38°C. Finally, flies with overexpression of *D. mojavensis* ortholog, which has 80% identity to GR28bD were not paralyzed in our experiments, suggesting that they are not temperature sensitive within 40°C. To test the thermosensitivity of the orthologs in a smaller neural network, we assayed for the ability of the orthologs to rescue GR28b mutant flies. GR28b mutants have no GR28b proteins and show deficits in detecting and avoiding noxious temperatures. We observed the avoidance behaviour of flies with overexpression of GR28bD or orthologs in Hot cells of GR28b mutants. In the thermosensitivity assay, one half of a chamber in the heat box was maintained at a reference temperature of 24°C while the temperature of the other half increased from 24-39°C in steps of 3°C every 60s. In contrast to mutant genetic controls, flies rescued with GR28bD or orthologs in the Hot cells had significantly high positive preference indices in the

thermosensitivity test, suggesting that they could detect and avoid high temperatures. Additionally, we are testing the temperature response properties of the orthologs in *D. melanogaster* motor neurons and in *Xenopus* oocytes, a heterologous system, to explore their possibilities of being used as thermogenetic tools.

Disclosures: **A. Mishra:** None. **A. Robinson:** None. **B.R. Berigan:** None. **M. Amirshenava:** None. **J.L. Lin:** None. **B.C. Zars:** None. **M. Milescu:** None. **L. Milescu:** None. **T. Zars:** None.

Poster

035. Sensory Transduction and Other Ion Channels

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Program #/Poster #: 035.09/D24

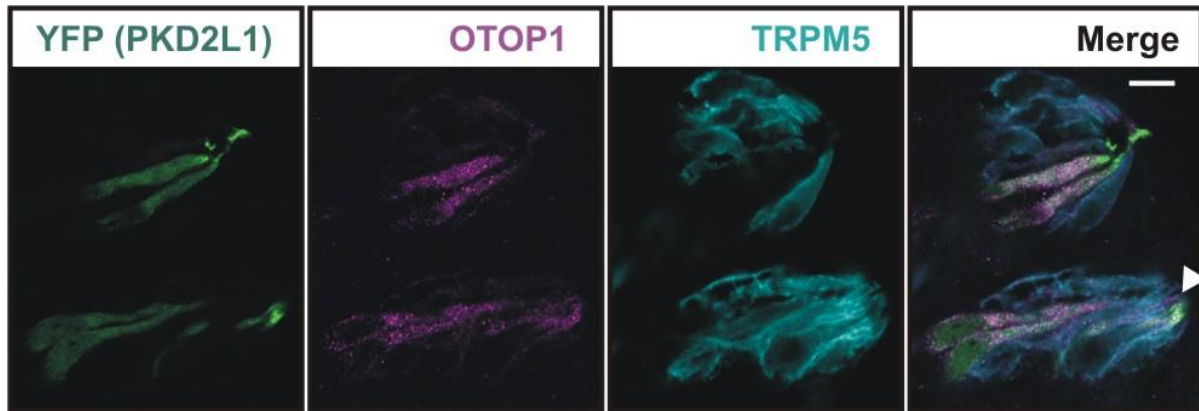
Topic: B.04. Ion Channels

Support: R01DC013741
R21DC012747

Title: Otop1 is expressed in taste cells that detect sour taste and necessary for their proton current

Authors: ***B. TENG**, Y.-H. TU, A. COOPER, H. TURNER, D. ARTIGA, E. R. LIMAN
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Abstract: Sour tastes are evoked in response to solutions of low pH, which activate a subset of taste receptor cells. These taste cells express PKD2L1 which although not the taste receptor, serves as a convenient marker for sour taste cells. Using a mouse in which the promoter of PKD2L1 drives expression of YFP, we previously showed that an inward current is evoked in response to lowering extracellular pH in sour taste cells but not other taste cells. We hypothesized that this proton current was carried by a proton-selective ion channel specifically expressed in sour taste cells. Through an RNAseq screen of genes enriched in sour taste cells, we have now identified Otopetrin1 (Otop1) as encoding a proton channel. Here we show that Otop1 is expressed in sour taste cells using single cell RNAseq, immunocytochemistry and in-situ hybridization. Recordings from HEK293 cells transfected with Otop1 show that the properties of the channel are similar to those observed in sour taste cells in terms of pH sensitivity and inhibition by extracellular Zn²⁺. To determine if Otop1 is required for the proton current in taste cells, we have recorded from taste cells isolated from circumvallate (CV) and fungiform (FF) papillae. These data show that proton currents are abolished in the absence of a functional Otop1 protein in mice carrying a mutation in their Otop1 gene. Thus we can conclude that Otop1 encodes the proton channel in taste cells and likely functions as a sour receptor.



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Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 035.10/D25

Topic: B.04. Ion Channels

Support: CIHR Grant FDN 143337

Heart and Stroke Foundation of Canada Grant G-16-00014197

Title: Salt loading enhances osmotic detection in rat magnocellular vasopressin neurons

Authors: *J. C. WYROSDIC¹, D. I. LEVI², M. PRAGER-KHOUTORSKY³, C. W. BOURQUE³

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Abstract: High dietary salt intake (HDSI) is a major risk factor for hypertension and is strongly correlated with the incidence of cardiovascular diseases and stroke. Increased osmotic pressure due to elevated plasma sodium levels are detected by osmosensitive neurons in the hypothalamus, called osmoreceptors. Osmoreceptors in the organum vasculosum laminae terminalis (OVLT) send an excitatory projection to the supraoptic nucleus (SON) and activate specialized magnocellular neurosecretory cells (MNCs), which are also intrinsically osmosensitive. These MNCs project to the neurohypophysis to release vasopressin (VP) into the circulation.

Recent studies have demonstrated that exposure to high dietary salt results in excessive activation of MNCs, leading to VP-mediated increases in blood pressure. Although this effect is

associated with a reduction in the efficacy of inhibitory synaptic signaling by baroreceptors, it remains possible that a facilitation of osmoreceptor signaling and/or intrinsic osmosensitiveness can also contribute to this process.

In this study, VP-eGFP Wistar rats were subjected to a 7-day salt-loading period in which their drinking water was replaced with 2% NaCl. Whole cell patch-clamp recordings of SON neurons were performed in both horizontal acute slice and in isolated cell preparations. Patched cells were exposed to an acute hyperosmotic stimulus in slices, or negative pressure in isolated cells. Current clamp analysis revealed that the excitatory response of VP MNCs to hypertonicity was enhanced following HDSI. Notably, the membrane depolarization induced by acute hypertonicity was greater in the rats subjected to 7-day 2% NaCl drinking water (SL) opposed to the euhydrated rats (EU). Additionally, voltage clamp analyses revealed no sensitization of afferent inputs to SON VP neurons following hyperosmotic stimulation. Current clamp analysis of isolated VP MNCs showed that reducing cell volume via application of negative pressure (-15 - -25mm hg) caused a significantly greater depolarization of the membrane potential in SL vs EU. Moreover, this effect was associated with a greater enhancement of action potential discharge frequency in SL animals. Lastly, the decrease cell volume prompted by a consistent amount of negative pressure was significantly smaller in the SL group. These results suggest that SL causes an enhancement of mechnosensitivity as well as an intrinsic osmosensitivity in VP MNCs.

Disclosures: J.C. Wyrosdic: None. D.I. Levi: None. M. Prager-Khoutorsky: None. C.W. Bourque: None.

Poster

035. Sensory Transduction and Other Ion Channels

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Program #/Poster #: 035.11/D26

Topic: B.04. Ion Channels

Support: MH002946

P41GM103712

P30DA035778

5R01GM099738

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

Authors: *D. TORRES-SALAZAR¹, A. M. KARA², M. H. CHENG³, A. D. GONZALEZ-SUAREZ⁴, J. GARCIA-OLIVARES¹, I. BAHAR³, S. G. AMARA²

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Abstract: Excitatory Amino Acid Transporters (EAATs) are responsible for clearing glutamate following its synaptic release, thus facilitating the precise transmission of excitatory signals in the brain. Failure to maintain tight control of extracellular glutamate concentrations can lead to neuronal cell death due to excitotoxicity. EAATs serve two functions: they work as secondary active transporters and as substrate-gated anion selective channel. In recent years, our understanding of the substrate transport mechanism has significantly advanced. However, the mechanism and molecular determinants for channel gating and anion permeation are only now emerging. Recent studies from our group combining molecular dynamics (MD) simulations and electrophysiological techniques have provided evidence for a structural coupling that controls the equilibrium between the transport cycle and anion channel opening. This work has supported the idea that channel gating occurs “outside” of the transport cycle from intermediate carrier conformations. A large body of evidence has demonstrated a critical role for C-terminal domains in the gating mechanism of voltage-dependent chloride channels. In EAATs, several studies have implicated C-terminal residues in cellular trafficking, localization and functionality. To investigate the possible contributions of the C-terminus of EAATs to anion channel gating, we constructed a computational model of EAAT4 including this region. Our computational model suggests potential interactions between charged residues in the C-terminus and in a conserved region of transmembrane domain 3 (TM3) that may be relevant to channel function. We tested this hypothesis using electrophysiological recordings in *Xenopus* oocytes expressing different point mutations in TM3 (K119D, R123D, and R127D) and the C-terminus (E523A/R and E528A/R) and using transporters with different C-terminal truncations. Our preliminary results demonstrate that truncation of the full C-terminus (Q521X) disrupts anion channel gating and significantly reduces glutamate transport, indicating that the C-terminal domain and its potential interaction with TM3 may play a critical role in modulating the structural coupling that control the equilibrium between substrate transport and anion channel opening. Moreover, mutations in both the TM3 and the C-terminus seem to significantly affect anion permeability ratios, suggesting a further role of the EAATs C-terminus modulating anion permeation. Our results provide new insight into the complex structural dynamics that link substrate translocation and anion channel gating in EAATs.

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Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 035.12/D27

Topic: B.04. Ion Channels

Title: Role of NALCN channels in pacemaking of substantia nigra dopamine neurons

Authors: *S. HAHN, S. KIM, H. KIM, M. PARK
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Abstract: Pacemaking of dopamine neurons in the substantia nigra pars compacta (SNc) requires sustained depolarization of membrane potential. Their resting membrane potential (RMP) is maintained between -55~-45 mV which is far from the equilibrium potential of K⁺ (E_k). Background Na⁺-permeable ion channels have been assumed to be essential for the establishment of RMP and pacemaking, and sodium leak channel (NALCN) appears to be a good candidate for basal Na⁺ leak currents. Therefore, we have investigated the role of NALCN in regulation of membrane potential 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. A nonselective cation channel blocker for TRPC channels, SKF96365, did not completely suppress background Na⁺ conductances. Despite the further usage of TTX and Cs⁺ which block Na_v and K_v channels, the substantial amount of Na⁺ leak conductances remained. But these remaining Na⁺ leak currents were attenuated by inhibition of NALCN channels. NALCN inhibition hyperpolarized membrane potential about 10 mV under the presence of TTX and ZD7288 which block Na_v and HCN channels. In addition, blockade of NALCN channel completely abolished pacemaking. Consistent with the previous reports that neurotensin (NT) activates NALCN channels, NT increased inward Na⁺ currents and tonic firing rates. These results suggest that NALCN could play an important role in the generation and regulation of pacemaker activities of the nigral dopamine neurons.

Disclosures: S. Hahn: None. S. Kim: None. H. Kim: None. M. Park: None.

Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 035.13/D28

Topic: B.04. Ion Channels

Support: CIHR
NSERC

Title: Structure-function analysis of pannexin-1's permeability to anandamide

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Abstract: Pannexin-1 (Panx1) belongs to the gap-junction family of membrane proteins that connect the intra- and extracellular spaces. It is a non-selective ion and metabolite permeable channel with broad tissue expression, including in excitatory neurons in the central nervous system. Although Panx1 is best known for its pathological roles, we recently described a novel role of Panx1 in regulating tissue levels of the endocannabinoid, anandamide (AEA) to control network excitability. We hypothesize that Panx1 functions as an AEA permeable channel that regulates fast uptake of AEA into neurons for clearance and degradation. To test this, we generated single point mutations of amino acids that are predicted to line Panx1's pore region from hydrophobic residues to polar serine residues, thus disrupting the potential hydrophobicity of the conduction pathway. Using a combination of cell-attached single channel recordings and fluorescent dye (sulforhodamine 101) flux through single channels, we are investigating if there is a site-specific requirement of pore-lining amino acids for AEA flux through Panx1. This will be accomplished using HEK293 cells transfected with the generated Panx1 mutants. We predict that mutating single or multiple hydrophobic amino acids will alter the AEA permeability of Panx1. Thus, a detailed analysis of Panx1's apparent lipid permeability will establish a structure/function level of understanding for the novel role of Panx1 as an endocannabinoid clearance pathway.

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Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

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Program #/Poster #: 035.14/D29

Topic: B.06. Synaptic Transmission

Support: DFG Grant: DE1154/5-1
DFG Grant: JA854/3-1

Title: Characterization of the interaction between connexin36 and CaMKII

Authors: *S. TETENBORG¹, S. HORMUZDI², H. MONYER³, G. VAN WOERDEN⁴, J. O'BRIEN⁵, U. JANSSEN-BIENHOLD⁶, K. DEDEK¹

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Abstract: Neuronal gap junctions formed by connexin36 (Cx36) and chemical synapses share striking similarities in terms of plasticity. Ca²⁺/calmodulin-dependent protein kinase II

(CaMKII), an enzyme known to induce memory formation, has recently been described to potentiate electrical coupling in the retina and several other brain areas via phosphorylation of Cx36. Although this mechanism is highly conserved across species, several aspects of it remain enigmatic: What is the exact CaMKII isoform that associates with Cx36 in the retina? Does CaMKII affect gap junction structure and association with interacting proteins? To address these questions, we used site-directed mutagenesis, transient transfections and histological analyses of CaMKII-B deficient retinas. In a first set of experiments, we identified the main CaMKII variants present at electrical synapses using isoform-specific antibodies. Among all four CaMKII isoforms only CaMKII-B and -D associated with Cx36. Surprisingly, colocalization with CaMKII-B was confined to a specific area of the inner retina and primarily associated with type 5 bipolar cell terminals, indicating that the kinase does only modulate a subset of retinal gap junctions. In addition we observed frequent colocalization of Cx36 and CaMKII-B with synaptic ribbons. This arrangement resembled the composition of mixed synapses, in which electrical coupling is regulated by glutamatergic activity. Given that CaMKII-B/Cx36 overlap was rather cell type-specific, we tested whether CaMKII affects Cx36 expression in type 5 bipolar cells and quantified the number and size of immunoreactive Cx36 puncta in CaMKII-B deficient retinas. These experiments revealed no significant differences between CaMKII KO and wildtype retinas. To further analyze the effects of CaMKII-induced phosphorylation on gap junction formation, we transfected phosphomimetic Cx36 mutants into HeLa cells. In line with our findings from CaMKII-B knockout retinas, phosphomimetic mutants displayed no obvious alterations in plaque formation and assembled into junctions of similar size to wildtype transfectants. Taken together, our data reveal the identity and exact localization of retinal CaMKII isoforms involved in plasticity of electrical synapses and suggest that their functions are dispensable for gap junction formation.

Disclosures: **S. Tetenborg:** A. Employment/Salary (full or part-time):; Part-time. **S. Hormuzdi:** None. **H. Monyer:** None. **G. van Woerden:** None. **J. O'Brien:** None. **U. Janssen-Bienhold:** None. **K. Dedek:** None.

Poster

035. Sensory Transduction and Other Ion Channels

Location: SDCC Halls B-H

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Program #/Poster #: 035.15/D30

Topic: B.04. Ion Channels

Support: NRF-2017R1A2B3011098
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IBS-R026-D1
the Brain Korea 21 (BK21) PLUS program

Title: The channel properties of alternatively spliced isoforms of anoctamin 2, calcium-activated chloride channels

Authors: *D. LEE¹, G. HA², E. CHEONG²

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Abstract: Calcium-activated chloride channels (CACCS) have critical functions in diverse biological systems. Driven by intra-cellular calcium signals, these channels codetermine cell excitability and regulate intra-cellular ion concentration. Also, these channels are responsible for many kinds of physiological functions including fluid secretion, muscle regulation, signal transduction, kidney osmole regulation and a fast block of polyspermy. Especially, recent studies show that anoctamin2 (ANO2), one of the calcium-activated chloride channels, contributes to some neuronal and physiological the brain functions: visual/olfactory transduction, hippocampal neuron response, melatonin secretion, cerebellar modulation of inhibitory transmission, striatal membrane potential oscillation, and mediating motor learning. At the molecular level, anoctamin2 has splice isoforms. However, channel properties among anoctamin2 isoforms and their physiological functions in the brain are unclear. In this study, channel properties of anoctamin2 isoforms are investigated using transfected cells. Therefore splice variants regulate activation and inactivation properties of the channel and responsible for current amplitude and rectification. It is expected to be responsible for different physiological functions in the brain and neuron.

Disclosures: D. Lee: None. G. Ha: None. E. Cheong: None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.01/D31

Topic: B.07. Synaptic Plasticity

Title: Long term potential, but not depression, in interlamellar hippocampus CA1

Authors: *H. KANG¹, H. TETTEH³, J. SU³, J. LEE³, S.-W. PARK⁴, J. KIM², J. JO⁵, S. YANG³, S. YANG¹

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Abstract: Synaptic plasticity in the lamellar CA3 to CA1 circuitry has been extensively studied while interlamellar CA1 to CA1 connections have not yet received much attention. One of our earlier studies demonstrated that axons of CA1 pyramidal neurons project to neighboring CA1 neurons, implicating information transfer along a longitudinal interlamellar network. Still, it remains unclear whether long-term synaptic plasticity is present within this longitudinal CA1 network. Here, we investigate long-term synaptic plasticity between CA1 pyramidal cells, using in vitro and in vivo extracellular recordings and 3D holography glutamate uncaging. We found that the CA1-CA1 network exhibits NMDA receptor dependent long-term potentiation (LTP) without direction or layer selectivity. By contrast, we find no significant long-term depression (LTD) under various LTD induction protocols. These results implicate unique synaptic properties in the longitudinal projection suggesting that the interlamellar CA1 network could be a promising structure for hippocampus-related information processing and brain diseases.

Disclosures: **H. Kang:** None. **H. Tetteh:** None. **J. Su:** None. **J. Lee:** None. **S. Park:** None. **J. Kim:** None. **J. Jo:** None. **S. Yang:** None. **S. Yang:** None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

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Program #/Poster #: 036.02/D32

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01MH109719
NIH Grant T32ES007026

Title: Fluorescent lifetime imaging microscopy of Type 1 Protein Phosphatase & I-2 interaction partners downstream of NMDA receptor stimulation

Authors: ***M. M. PAPASERGI-SCOTT**, H. HOU, K. F. FOLEY, H. XIA
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Abstract: The N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor located postsynaptically on excitatory neurons. Regulation of ERK and CREB (cAMP/calcium response element-binding) proteins occurs in a phosphorylation-dependent manner downstream of NMDAR. In neurons of the hippocampus and cortex, Type 1 Protein Phosphatase (PP1) is specifically activated downstream of synaptic NMDAR and functions to inhibit CREB-mediated gene transcription that is involved in long-term modifications of the synapse. Currently, the regulation of PP1 activities in this process is not fully understood. Studies on the interaction of PP1 regulation by protein Inhibitor-2 (I-2) have shown I-2 binding to PP1 contributes to synaptic NMDAR-mediated long-term depression (LTD). We hypothesize I-2 acts within a larger complex to bind and regulate PP1. We have sought to identify novel interacting proteins that

associate with PP1 bound to I-2 and characterize the signaling pathways downstream of these complexes. As a vital component of this study, we have utilized fluorescent lifetime imaging microscopy (FLIM). The use of FLIM coupled with two-photon microscopy allows for the recording of dynamic changes in protein-protein interactions in real-time through comparison of the exponential decay rate of tagged-fluorophores in the excited state. The reliance on fluorescence decay rather than fluorescence intensity decreases the noise from background fluorescence, therefore, allowing for more accurate localization information. We have developed an array of fluorescently tagged constructs of PP1, I-2, as well as known and putative interacting partners. Primary cultures of embryonic rat cortical neurons were transfected at *in vitro* day 14 using fluorophore-tagged constructs. The neurons were then visualized over-time using 2-photon microscopy coupled with FLIM under conditions of NMDA treatment. Our exploratory study has provided proof-of-principle for the technique's use with our protein constructs and also provided evidence of novel interaction partners and complexes for further study.

Disclosures: M.M. Papasergi-Scott: None. H. Hou: None. K.F. Foley: None. H. Xia: None.

Poster

036. Long-Term Depression (LTD)

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

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Topic: B.07. Synaptic Plasticity

Support: FCT/PhD Fellow SFRH/BD/52228/2013

FCT PTDC/BIM-MEC/47778/2014

DFG Center for Nanoscale Microscopy and Molecular Physiology of the Brain

LISBOA-01-0145-FEDER-007391

iFCT

Title: mGluR5-dependent NMDAR activation is associated with LTD shift upon aging

Authors: *M. T. FERREIRA¹, D. G. FERREIRA^{2,1}, R. GOMES^{1,3}, J. E. COELHO¹, M. BADER^{4,5,6}, D. BLUM⁷, T. F. OUTEIRO^{2,8,9}, H. MARIE¹⁰, P. A. POUSINHA¹⁰, L. V. LOPES¹
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Abstract: Synaptic dysfunction plays a central role in Alzheimer's Disease (AD), since it drives the cognitive decline. Importantly, the adenosine A_{2A} receptor (A_{2A}R) encoding gene was recently associated to hippocampal volume in Alzheimer's disease patients (Horgusluoglu-Moloch *et al*, 2017, Neurobiol. Aging). A_{2A}R blockade decreases the risk of developing memory impairments in human aging and AD through caffeine (van Boxtel *et al*, 2003, Pharmacol. Biochem. Behav.; Ritchie *et al*, 2007, Neurology) and prevents hippocampus-related impairments in animal models of aging and AD, namely LTP (Batalha *et al*, 2013, Mol. Psychiatry; Laurent *et al*, 2015, Mol. Psychiatry; Vieira da Silva *et al*, 2016, Nat. Comm). Consequently, hippocampal A_{2A}R dysregulation is associated to synaptic dysfunction in aging and AD. In this study, we explore the synaptic function of A_{2A}R in age-related conditions. We report, for the first time, a significant overexpression of A_{2A}R in hippocampal neurons of aged humans, which is aggravated in AD patients. A similar profile of A_{2A}R overexpression in rats [tg(CaMKII-hA_{2A}R)] was sufficient to drive age-like memory impairments in young animals and to uncover a hippocampal LTD-to-LTP shift. This LTD shift was rescued by A_{2A}R blockade and was accompanied by increased NMDA receptor gating, dependent on mGluR5 and associated to enhanced Ca²⁺ influx. Calcium-evoked variations in neuronal cultures transfected with A_{2A}R were dependent of NMDAR and mGluR5 activation. We confirmed the same plasticity shift in memory-impaired aged rats and APP/PS1 mice modelling AD, which was rescued upon A_{2A}R blockade. This newly found interaction might prove a suitable alternative for regulating aberrant mGluR5/NMDAR signaling in AD without disrupting their constitutive activity.

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Poster

036. Long-Term Depression (LTD)

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.04/D34

Topic: B.07. Synaptic Plasticity

Support: IBRO USCRC Research fellowship

Title: Metabotropic glutamate receptor (mGluR) mediated long term depression in young and adult C57BL/6 mice

Authors: *A. J. IDOWU¹, A. KIRKWOOD²

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Abstract: Recently, the neurobehavioral characterization of C57BL/6 mice from young to middle-age showed significant changes from young through middle age. Although, preserved cognitive function during normal aging in rats has been shown to be associated with metabotropic glutamate receptor (mGluR) mediated plasticity, the unique functional properties of this form of plasticity in the C57BL/6 mice are yet to be described. Therefore we investigated mGluR mediated long term depression in young (1 to 3 months old; n=12) and adult (6 to 8 months old; n=12) C57BL/6 mice. Our findings showed an increase in the magnitude of mGluR long term depression between young and adult C57BL/6 mice. This finding suggests a shift in mGluR plasticity mechanisms in the C57BL6 mice during the early phase of the normal aging process.

Disclosures: **A.J. Idowu:** None. **A. Kirkwood:** None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.05/D35

Topic: B.07. Synaptic Plasticity

Support: CIHR

Title: Pannexin-1 contributes to long-term depression at the CA3-CA1 synapse

Authors: ***A. WERNER**¹, R. J. THOMPSON²

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Abstract: Synaptic plasticity is the ability of differing levels of activity to alter the strength of a synapse. Long-term changes in synaptic strength are thought to be the major components of learning and memory. One such change is long-term depression (LTD), which is characterized as a long-lasting decrease in synaptic strength. The classical model of LTD induction postulates that modest calcium influx through the NMDA receptor (NMDAR) activates a protein phosphatase cascade that ultimately leads to the removal of AMPA receptors from the synapse, causing an overall decrease in synaptic strength. Recently this classic model of LTD induction was challenged (Nabavi et al. 2013). Rather than Ca²⁺ influx through the NMDAR, LTD may instead require metabotropic signaling by the NMDAR. Our group has reported that NMDAR overstimulation during excitotoxicity induces metabotropic NMDAR activity involving Src family kinases (SFKs) and phosphorylation/activation of pannexin-1 (Panx1) ion and metabolite channels. Therefore, we hypothesized that Panx1 may be a downstream target of metabotropic NMDAR-induced LTD. Using whole cell patch clamp electrophysiology, we induced LTD in CA1 pyramidal neurons with low-frequency stimulation (LFS; 3Hz, 900 pulses) to the Schaffer collaterals. Inhibition of NMDAR metabotropic signaling with APV completely prevented LTD

induction ($103.1 \pm 96 \pm 8.7\%$), whereas application of MK-801 to prevent NMDAR ionotropic signaling had only a slight reduction in LTD ($70.4 \pm 11.6\%$) as opposed to control conditions ($46.8 \pm 23.7\%$). Panx1 inhibition with a mimetic peptide (10 panx) showed a complete block in LTD induction ($116.1 \pm 22.7\%$). LTD was also blocked with SFK inhibition ($134.7 \pm 57.7\%$). Further evaluation of a known SFK phosphorylation site (Y308) on the C-terminus of Panx1, using the TAT-Panx₃₀₈ peptide, revealed a similar inhibition in LTD ($94.3 \pm 15.0\%$). Together this suggests NMDAR-LTD may require metabotropic signaling by the NMDAR through SFKs and the activation of Panx1.

Disclosures: A. Werner: None. R.J. Thompson: None.

Poster

036. Long-Term Depression (LTD)

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Program #/Poster #: 036.06/D36

Topic: B.07. Synaptic Plasticity

Support: PSL Research University Grant MyoSynapse

Title: Actomyosin-mediated nanostructural remodeling of the presynaptic vesicle pool by cannabinoids induces long-term depression

Authors: M. MCFADDEN¹, H. XU², Y. CUI², R. A. PISKOROWSKI³, C. LETERRIER⁴, D. ZALA¹, L. VENANCE², V. CHEVALEYRE³, *Z. LENKEI¹

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Abstract: Endo- and exocannabinoids, such as the psychoactive component of marijuana, exert their effects on brain function by inducing several forms of synaptic plasticity through the modulation of presynaptic vesicle release. However, the molecular mechanisms underlying the widely expressed endocannabinoid-mediated long-term depression (eCB-LTD), are poorly understood. Here, we reveal that eCB-LTD depends on the contractile properties of the presynaptic actomyosin cytoskeleton. Preventing this contractility, both directly by inhibiting non-muscle myosin II NMII ATPase and indirectly by inhibiting the upstream Rho-associated kinase ROCK, abolished long-term, but not short-term forms of cannabinoid-induced functional plasticity in both inhibitory hippocampal and excitatory cortico-striatal synapses. Furthermore, using 3D superresolution microscopy, we find an actomyosin contractility-dependent redistribution of synaptic vesicle pools within the presynaptic compartment following cannabinoid receptor activation, leading to vesicle clustering and depletion from the pre-synaptic active zone. These results suggest that cannabinoid-induced functional plasticity is mediated by a nanoscale structural reorganization of the presynaptic compartment produced by actomyosin

contraction. By introducing the contractile NMII as an important actin binding/structuring protein in the dynamic regulation of synaptic function, our results open new perspectives in the understanding of mechanisms of synaptic and cognitive function, marijuana intoxication and psychiatric pathogenesis.

Disclosures: **M. McFadden:** None. **H. Xu:** None. **Y. Cui:** None. **R.A. Piskorowski:** None. **C. Leterrier:** None. **D. Zala:** None. **L. Venance:** None. **V. Chevaleyre:** None. **Z. Lenkei:** None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.07/D37

Topic: B.07. Synaptic Plasticity

Title: Depolarization induced suppression of excitation mediated by endocannabinoids in the hyperdirect pathway of the basal ganglia

Authors: ***L. GORODETSKI**, A. KORNGREEN
Bar-Ilan Univ., Ramat Gan, Israel

Abstract: The rodent entopeduncular nucleus (EP) is one of the output nuclei of the basal ganglia. EP neurons receive GABAergic inputs from the striatum via the direct pathway of the basal ganglia, and from the GP via the indirect pathway. Furthermore, the EP receives glutamatergic input arriving down the hyperdirect pathway from the cortex via the subthalamic nucleus (STN).

Long term depression (LTD) has been observed in many synapses in the basal ganglia. Both Hebbian and non-Hebbian forms of LTD can be induced at the glutamatergic inputs arriving from the cortex to spiny projection neurons (SPNs) the striatum. In direct and indirect pathway LTD has been induced by high-frequency stimulation of cortical inputs to the striatum. This form of LTD requires activation of postsynaptic voltage-gated calcium channels, metabotropic glutamate receptors that leading to the synthesis of endocannabinoids which bind to presynaptic receptors. LTD of glutamatergic synapses has been observed also in the hyperdirect pathway between the cortex and the STN, between the STN and dopaminergic neurons of the SNc, and between the STN and GABAergic neurons in the SNr.

We hypothesized that depolarization of postsynaptic neurons can induce long-term changes to the STN->EP synapse. To investigate this hypothesis we recorded in whole-cell mode from EP neurons while electrically stimulating the STN. Post-synaptic high frequency stimulation generated robust LTD in the STN->EP synapse. Whereas, stimulation at moderate frequencies generated only mild LTD.

In order to investigate if post-synaptic stimulation generated LTD leads to the synthesis of endocannabinoids which bind to presynaptic receptors, we applied AM251 which is antagonist

of CB1 receptors that blocked the LTD.

In conclusion, we show that depolarization induced suppression of excitation in the STN-EP synapses is depend on the frequency of the APs of the stimulation in the postsynaptic site and is mediate by endocannabinoids.

Disclosures: L. Gorodetski: None. A. Korngreen: None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.08/D38

Topic: B.07. Synaptic Plasticity

Support: HKRGC-GRF 17113717

Title: Cannabinoid receptor suppresses long-term depression in the neonatal brain for consolidation of neuronal circuits for spatial cognition

Authors: *Y.-S. CHAN^{1,2}, C.-W. MA¹, W. SHI¹, D.-Y. SHUM^{1,2}

¹Sch. of Biomedic. Sci., Fac. Med., Univ. Hong Kong, Hong Kong, China; ²State Key Lab. of Brain and Cognitive Sciences, Univ. Hong Kong, Hong Kong, China

Abstract: Reduction in the efficacy of induction of long-term depression (LTD) of inhibitory transmission has emerged as a key feature of circuit consolidation. We demonstrate that the endocannabinoid (eCB) system facilitates induction of long-term depression (LTD) of inhibitory transmission in the vestibular nucleus (VN). We found downregulation of cannabinoid receptor type I (CB1R) accompanies developmental decrease of LTD induction efficacy from 70% at P5-7 to 20% after P9. This coincides with emergence of graviceptive negative geotaxis reflex at P9. Blockade of CB1R in the neonatal critical period for VN development decreased LTD induction efficacy to 40% and accelerated emergence of graviceptive reflex from P9 to P7, while activation of CB1R delayed it to P13. Furthermore, chronic activation of CB1R in rats during the neonatal stage precluded development of navigational skills in the adult. These findings highlight eCB as an important regulator of GABAergic transmission efficacy in the VN via the modulation of LTD and regulates developmental consolidation of vestibular circuitry. The results further suggest that adolescent exposure to cannabinoids may have a permanent detrimental effect on the development of brain circuits. (This work is supported by HKRGC-GRF 17113717)

Disclosures: Y. Chan: None. C. Ma: None. W. Shi: None. D. Shum: None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.09/D39

Topic: B.07. Synaptic Plasticity

Support: NIH grant R00 AA023507

Title: Alcohol exposure disrupts mu opioid receptor-mediated long-term depression at insular cortex inputs to dorsolateral striatum

Authors: ***B. MUÑOZ**, B. M. FRITZ, F. YIN, B. K. ATWOOD
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Abstract: Drugs of abuse, including alcohol, ablate the expression of specific forms of long-term synaptic depression (LTD) at glutamatergic synapses in dorsal striatum (DS), a brain region involved in goal-directed and habitual behaviors. This loss of LTD is associated with altered DS-dependent behavior. Given the role of the μ -opioid receptor (MOR) in behavioral responding for alcohol, we explored the impact of alcohol on various forms of MOR-mediated synaptic depression that we find are differentially expressed at specific DS synapses. Corticostriatal MOR-mediated LTD (mOP-LTD) in the dorsolateral striatum occurs exclusively at inputs from anterior insular cortex and is selectively disrupted by in vivo alcohol exposure. Alcohol has no effect on corticostriatal mOP-LTD in dorsomedial striatum, thalamostriatal MOR-mediated short-term depression, or mOP-LTD of cholinergic interneuron-driven glutamate release. Disrupted mOP-LTD at anterior insular cortex-dorsolateral striatum synapses may therefore be a key mechanism of alcohol-induced neuroadaptations involved in the development of alcohol use disorders.

Disclosures: **B. Muñoz:** None. **B.M. Fritz:** None. **F. Yin:** None. **B.K. Atwood:** None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.10/D40

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS092381

Title: Induction of LTD in the indirect pathway improves motor symptoms in Parkinsonian mice

Authors: *C. ABBURI¹, B. RODRIGUEZ¹, X. ZHUANG², D. MCGEHEE¹

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease and nearly 60,000 Americans are diagnosed with PD every year. Degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and eventual loss of dopamine (DA) in the striatum induces the motor deficits observed in PD patients. Dopamine in the dorsolateral striatum (DLS) differentially modulates corticostriatal synaptic plasticity at D1 receptor expressing medium spiny neurons (D1-MSNs) of the direct pathway and D2-receptor expressing MSNs (D2-MSNs) of the indirect pathway. In the 6-OHDA mouse model of PD, decreased DA innervation of the DLS results in aberrant plasticity of corticostriatal synapses. Our previous findings suggest that D2-receptor blockade induces aberrant motor learning through the potentiation of corticostriatal synapses of the indirect pathway. We are testing whether the induction of synaptic depression in the indirect pathway can reverse the aberrant plasticity at D2-MSNs, and ameliorate motor symptoms in a mouse model of PD. To this end, mice were trained on the accelerating rotarod and then subjected to a unilateral intra-striatal 6-OHDA injection. The lesion leads to impaired rotarod performance and apomorphine-induced rotational behavior, consistent with unilateral loss of striatal dopamine. We then induced synaptic depression at corticostriatal synapses of D2-MSNs using optogenetic stimulation combined with systemic administration of the D2 agonist quinpirole (5 mg/kg; i.p). Channelrhodopsin-2 was expressed using viral vector infection in the forelimb region of M1 motor cortex 6 weeks prior to the stimulation protocol. Fiberoptic implants targeting the lesioned hemisphere of the DLS were used to deliver 20 Hz stimulation of 10 msec light pulses for 30 min/day on 5 consecutive days to induce long-term depression (LTD) at these synapses. This stimulation paradigm paired with quinpirole improved motor performance on the accelerating rotarod. These data suggest that reversing 6-OHDA-induced aberrant corticostriatal plasticity in the indirect pathway is therapeutically beneficial in relieving the motor symptoms of PD.

Disclosures: B. Rodriguez: None. X. Zhuang: None. D. McGehee: None.

Poster

036. Long-Term Depression (LTD)

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 036.11/D41

Topic: B.07. Synaptic Plasticity

Support: Mentoring environment grant (MEG)
NIDA grant R15dA038092

Title: Acute and chronic cocaine exposure occludes long-term depression in ventral tegmental area GABA neurons

Authors: *B. WU¹, L. N. FRIEND³, J. G. EDWARDS²

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Abstract: The ventral tegmental area in the midbrain modulates reward processing. Drugs of abuse can increase midbrain dopamine (DA) activity, and can alter ventral tegmental area glutamate plasticity, leading to addiction. While DA neurons are the principal mediator of reward, their activity is regulated by nearby VTA GABA cells. Our lab has demonstrated a form of pre-synaptic CB1-dependent long-term depression of glutamatergic inputs onto VTA GABA neurons. This plasticity is dependent on mGluR5 and post-synaptic diacylglycerol lipase alpha. Δ^9 -tetrahydrocannabinol, the active ingredient in marijuana initiates long-term depression at this synapse by acute slice application, and occludes this plasticity following chronic injections. Our aim for this study was to determine whether cocaine can also influence the plasticity of this excitatory synapse. We recorded excitatory inputs on GABA cells using whole cell voltage-clamp electrophysiology in VTA slices of GAD67 mice. We found that both acute and chronic injections of cocaine were sufficient to occlude long-term depression. The plasticity observed, however, can be reversed to the naïve state, as long-term depression was again observed following 7 days of abstinence. Furthermore, chronic cocaine application decreased AMPA/NMDA ratios, compared to vehicle-only injections, which is the opposite to the change occurring at glutamatergic inputs to VTA DA cells. Since this novel form of cocaine-evoked plasticity of VTA GABA cells can depress excitatory inputs, it could potentially cause disinhibition of nearby dopamine neurons.

Disclosures: B. Wu: None. L.N. Friend: None. J.G. Edwards: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.01/D42

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS091546

Title: A glutamate homeostat controls the presynaptic inhibition of neurotransmitter release

Authors: *D. K. DICKMAN, X. LI, P. GOEL
Neurobio., USC, Los Angeles, CA

Abstract: We have interrogated the synaptic dialogue that enables the bi-directional, homeostatic control of presynaptic efficacy at the glutamatergic *Drosophila* neuromuscular junction (NMJ). We find that homeostatic depression and potentiation utilize disparate genetic, induction, and expression mechanisms. Specifically, homeostatic potentiation is achieved through reduced CaMKII activity postsynaptically and increased abundance of active zone material presynaptically at one of the two neuronal subtypes innervating the NMJ, while homeostatic depression occurs without alterations in CaMKII activity and is expressed at both neuronal subtypes. Further, homeostatic depression is only induced through excess presynaptic glutamate release and operates with complete disregard to the postsynaptic response. We propose that two independent homeostats modulate presynaptic efficacy at the *Drosophila* NMJ: one is an inter-cellular signaling system that potentiates synaptic strength following diminished postsynaptic excitability, while the other adaptively modulates presynaptic glutamate release through an autocrine mechanism without feedback from the postsynaptic compartment.

Disclosures: **D.K. Dickman:** None. **X. Li:** None. **P. Goel:** None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.02/D43

Topic: B.07. Synaptic Plasticity

Support: NS091546

Title: Impacts of injury-related signaling on synaptic function and homeostatic plasticity

Authors: ***P. GOEL**, D. DICKMAN
Neurobio., USC, Los Angeles, CA

Abstract: Synapses are endowed with the stability to last for a lifetime, yet sufficiently plastic to change and adapt with experience. This flexibility is particularly important during injury, when synaptically connected but uninjured cells must respond while still maintaining functionality. Although fundamental signaling pathways that mediate intrinsic neuronal injury responses have been defined, less is known about how uninjured synaptic targets respond. We have investigated the structure, function and plasticity of the postsynaptic cell following presynaptic activation of the injury-related Dual Leucine Zipper Kinase (DLK) pathway at the *Drosophila* neuromuscular junction. We find that the postsynaptic compartment reduces neurotransmitter receptor levels, thus depressing synaptic strength. Interestingly, this diminished state is stabilized through distinct modulations to two postsynaptic homeostatic signaling systems. First, a retrograde response normally triggered by reduced receptor levels is silenced, preventing a compensatory enhancement in presynaptic neurotransmitter release. However, when global presynaptic release

is attenuated, a postsynaptic receptor scaling mechanism persists to adaptively stabilize this diminished neurotransmission state. Thus, the homeostatic set point of synaptic strength is recalibrated to a reduced state as synapses acclimate to injury. We are currently using a translational profiling approach to define the changes in gene expression and translation induced in neurons during DLK signaling to identify the downstream signaling pathways of this adaptive stress response system in neurons. We are also using this approach to reveal adjustments in the postsynaptic muscle in response to active DLK signaling in motor neurons.

Disclosures: P. Goel: None. D. Dickman: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.03/D44

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS091546
UAS WISE

Title: Synapse-specific and compartmentalized induction and expression of presynaptic homeostatic potentiation

Authors: *X. LI¹, P. GOEL², C. CHEN², V. ANGAJALA¹, X. CHEN², D. K. DICKMAN³
²Dept. of Neurobio., ³Neurobio., ¹USC, Los Angeles, CA

Abstract: Postsynaptic compartments can be specifically modulated during various forms of synaptic plasticity, but it is unclear whether this precision is shared at presynaptic terminals. Presynaptic Homeostatic Plasticity (PHP) stabilizes neurotransmission at the *Drosophila* neuromuscular junction, where a retrograde enhancement of presynaptic neurotransmitter release compensates for diminished postsynaptic receptor functionality. To test the specificity of PHP induction and expression, we have developed a genetic manipulation to reduce postsynaptic receptor expression at one of the two muscles innervated by a single motor neuron. We find that PHP can be induced and expressed at a subset of synapses, over both acute and chronic time scales, without influencing transmission at adjacent release sites. Further, homeostatic modulations to CaMKII, vesicle pools, and functional release sites are compartmentalized and do not spread to neighboring pre- or post-synaptic structures. This demonstrates that both PHP induction and expression mechanisms are locally transmitted and restricted to specific synaptic compartments. Current efforts are focused on defining how components of the active zone are specifically remodeling during PHP, and on identifying the key machinery in the postsynaptic cell that drives the synapse-specific retrograde signal.

Disclosures: X. Li: None. P. Goel: None. C. Chen: None. V. Angajala: None. X. Chen: None. D.K. Dickman: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.04/D45

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01NS085164

NSF Grant 1557792

Whitehall Foundation Grant 2014-08-03

Title: Uncoupling the maintenance and rapid induction of homeostatic synaptic plasticity

Authors: *T. D. JAMES, D. J. ZWIEFELHOFER, C. FRANK

Dept. of Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

Abstract: Normal central nervous system function depends on stable and reliable synapse function. Forms of homeostatic synaptic plasticity (HSP) maintain this stability by correcting for perturbations and restoring output to physiological levels. However, our incomplete knowledge of these homeostatic signaling pathways limits our understanding of neurological disorders defined by a lack of synapse stability. In order to better address this knowledge gap, we use the *Drosophila melanogaster* larval neuromuscular junction (NMJ) as a model glutamatergic synapse. At the NMJ, impaired post-synaptic glutamate receptor function (reduced quantal size) initiates a retrograde, muscle-to-nerve signaling cascade that restores synaptic output by increasing neurotransmitter release (quantal content). In response to chronic impairments of glutamate receptor function, such as the *GluRIIA*^{SP16} loss-of-function mutation or *GluRIII* RNAi, synapses continually maintain HSP. In contrast, synapses rapidly induce HSP following acute blockade of glutamate receptors with the wasp venom Philanthotoxin-433 (PhTox). Although the two processes seem to largely share the same molecular machinery, molecules such as C-Terminal Src Kinase (Csk), Target of rapamycin (Tor), or Ephexin (Exn), are required only for the maintenance of HSP. With this in mind, we sought to determine whether the HSP maintenance and induction processes were separable. First we show that *Phospholipase C 21C* (*Plc21C*), a PLC β homologue, is required for the maintenance of HSP but not its rapid induction. Next we show that applying PhTox to *GluRIII* RNAi synapses resulted in both a further reduction in quantal size and additional potentiation of quantal content, indicating that both forms of HSP were simultaneously active. Surprisingly, we found that the failure to maintain HSP at *GluRIII* RNAi + *Plc21C* RNAi synapses did not preclude its rapid induction. Using genetic and pharmacological approaches, we showed that these discreet HSP signaling requirements hold true for other molecules in the PLC β signaling pathway, including inositol

trisphosphate (IP3) and the IP3 receptor (IP3R). Because the two processes are molecularly separable, we propose that the rapid induction of HSP requires only a subset of molecules requires for its maintenance.

Disclosures: T.D. James: None. D.J. Zwiefelhofer: None. C. Frank: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.05/D46

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS090644

Title: Trans-synaptic signaling underlying presynaptic homeostatic potentiation at the mouse neuromuscular junction

Authors: *A. E. HOMAN¹, S. D. MERINEY²

¹Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; ²Univ. Pittsburgh, Pittsburgh, PA

Abstract: Presynaptic homeostatic potentiation, the increase in presynaptic strength in response to a reduction of postsynaptic activity, is a mechanism by which a synapse can maintain a proper set point of neurotransmitter release. This phenomenon has been studied extensively at the drosophila neuromuscular synapse (NMJ) and a host of mechanisms have been identified to mediate the increase in synaptic strength including, upregulation of presynaptic voltage gated calcium channels (VGCCs) and an increase in the size of the ready-releasable pool of vesicles. At the Drosophila NMJ, several trans-synaptic signals by which the postsynaptic muscle fiber can relay the reduction of activity to the presynaptic motoneuron have been identified and include extracellular matrix and innate immune signaling pathways. Presynaptic homeostatic potentiation has also been demonstrated at the mammalian NMJ, though the mechanisms mediating the increase in synaptic strength are less well studied. Brain-derived neurotrophic factor (BDNF) is a well-characterized signaling system at the vertebrate neuromuscular junction that is believed to control tonic neurotransmitter release. BDNF has been demonstrated to be released in an activity dependent manner from the postsynaptic muscle cell, making it an attractive target as a trans-synaptic signaling pathway underlying homeostatic potentiation. We found that presynaptic homeostatic potentiation was induced following a one-hour partial blockade of postsynaptic acetylcholine receptors (AChRs) with α -Bungarotoxin (BTX). Further, this potentiation could also be induced by chelating postsynaptic calcium with BAPTA, suggesting this phenomenon may be dependent on calcium concentration in the muscle cell. Further, block of BDNF receptors (trkB) occluded presynaptic homeostatic potentiation, suggesting that BDNF signaling may be one of the trans-synaptic signals underlying the

homeostatic increase in neurotransmitter release. These data place a well-established signaling system at the mouse NMJ into a novel context and identify new targets for the control of synaptic strength.

Disclosures: A.E. Homan: None. S.D. Meriney: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.06/D47

Topic: B.07. Synaptic Plasticity

Support: A*STAR International Fellowship
CIHR Foundation Grant FDN-154286

Title: The role of netrin 1-DCC signaling in regulating GABA_AR homeostatic plasticity

Authors: *E. CHAN, Y. WANG

Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The adaptive ability of neurons to modify their strengths in accordance to stimuli is known as synaptic plasticity. Homeostatic plasticity is a negative feedback mechanism that neurons utilize to maintain their level of excitability. Over the past decade, homeostatic plasticity in the excitatory synapses has been extensively studied. In contrast, the underlying mechanism of homeostatic plasticity in the inhibitory synapses remains largely overlooked. We had established a robust model for the study of GABA_AR homeostatic plasticity in primary neurons. By using this model, we found that neuronal depolarization by blockade of GABA_ARs for one hour significantly increased GABA_AR-mediated transmission, as evident by the increased amplitude and frequency of miniature inhibitory postsynaptic currents (mIPSCs). These results suggest that GABA_AR homeostatic plasticity in matured neurons is a tightly regulated process and likely to occur through an increased function and/or number of cell surface GABA_ARs. Using membrane fractionation followed by immunoblotting, we observed that the increase in GABA_ARs during homeostatic plasticity was localized within the postsynaptic membrane, without altering the total number of the receptor on the cell surface. Interestingly, we found that the increase in GABA_ARs was coincided with an increase in netrin 1 detected in the extracellular media. Furthermore, bath application of netrin 1 mimicked neuronal depolarization, resulting in the increased amplitude and frequency of mIPSCs, as well as increased GABA_AR expression at the postsynaptic membrane. Consistent with a critical role of netrin 1 in mediating this homeostatic synaptic scaling at the GABAergic synapse, we also detected DCC, one of the netrin 1 receptors, to be localized in close proximity to GABA_ARs at the inhibitory synapses. Taken together, our

preliminary data suggests the novel role of netrin 1 as a diffusible regulator of GABA_AR homeostatic plasticity.

Disclosures: E. Chan: None. Y. Wang: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.07/D48

Topic: B.07. Synaptic Plasticity

Support: R01 NS065992

Title: Homeostatic synaptic plasticity in embryonic motoneurons is dependent on TNF alpha signaling

Authors: *C. E. GONZALEZ-ISLAS^{1,2}, M. A. GARCÍA-BEREGUIAIN^{1,3}, C. LINDSLY¹, P. WENNER¹

¹Emory Univ. Sch. of Med., Atlanta, GA; ²Doctorado en Ciencias Biológicas, Univ. Autónoma de Tlaxcala, Tlaxcala, Mexico; ³Yachay Tech. Univ., Urcuqui, Ecuador

Abstract: The role of the proinflammatory cytokine TNF- α ; in normal physiology, acute and chronic inflammation, cancer-related inflammation, and autoimmune disease have been known for many years. However, a variety of roles for TNF- α have also been found in the homeostasis and pathology in the central nervous system. In particular, it has been implicated in homeostatic synaptic scaling, where miniature excitatory postsynaptic current (mEPSC) amplitudes are increased across their entire distribution. Under certain conditions, reductions in spiking activity lead to glial release of TNF- α , causing an increase in cell-surface expression of excitatory GluA2-lacking glutamate receptors and the endocytosis of inhibitory GABA_A receptors (GABARs) thereby increasing neuronal excitability. We have previously reported that 2-day blockade of GABARs *in vivo* in the chick embryo triggers a scaling up of AMPA receptors through insertion of GluA2-lacking glutamate receptors and GABAergic upscaling through changes in the chloride gradient in motoneurons. Here we test whether TNF- α , mediates AMPA and/or GABA upscaling in embryonic motoneurons. We found that the continuous presence of exogenous TNF- α in the isolated embryonic spinal cord produced an upscaling of both AMPA- and GABAergic synapses. In addition, we treated embryos *in vivo* for 2 days with a combination of antagonists to GABA_A receptors (gabazine 10 μ M) and TNF- α receptors (Enbrel or Xpro) and found that GABA- and AMPAergic scaling was prevented when TNF- α signaling was blocked. The findings suggest that TNF- α receptor activation is necessary for this scaling to occur in the living embryo. In contrast to the mechanisms of GABAergic downscaling in cultured neurons (GABAR trafficking), we found in embryonic motoneurons that TNF- α -mediated GABAergic

upscaling was produced by changes in the chloride gradient, suggesting a possible role of TNF- α as modulator of the intracellular chloride homeostasis during development.

Disclosures: C.E. Gonzalez-Islas: None. M.A. García-Bereguain: None. C. Lindsly: None. P. Wenner: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

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Program #/Poster #: 037.08/D49

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01NS085164

NSF Grant 1557792

Whitehall Foundation Grant 2014-08-03

Title: The transition between the induction and maintenance of homeostatic synaptic signaling

Authors: K. M. LEMBKE, A. M. SPRING, *C. FRANK

Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

Abstract: Forms of homeostatic synaptic plasticity (HSP) stabilize neuronal and circuit activities. For several years, HSP was thought to be a slow acting form of neuroplasticity. However, work at model synapses like the *Drosophila melanogaster* neuromuscular junction (NMJ) has shown that homeostatic signaling systems can be induced within an acute timescale (seconds to minutes) and maintained throughout development. At the NMJ, genetic and pharmacological manipulations can decrease the sensitivity of postsynaptic receptors to single vesicles of neurotransmitter. The resulting decrease in quantal size triggers retrograde signaling that drives increased neurotransmitter release. As a result, evoked postsynaptic responses remain steady. Published data have suggested that acutely induced homeostatic signaling processes and chronically maintained processes converge upon the same presynaptic targets. It is unclear how this convergence works. In particular, it is unclear if the maintenance of homeostatic signaling at the NMJ is independent of its induction - or if it is simply a continuation of induction. Through genetic screens and follow-up work, we found that several factors residing in the postsynaptic muscle support in the long-term maintenance of HSP, but not its short-term induction. Among them are tyrosine kinases C-terminal Src Kinase (Csk), Fibroblast Growth Factor Receptor Heartless (Htl/FGFR), and a Src Family Kinase member (Src64B). We have also documented that long-term HSP signaling at the NMJ is a reversible signaling process that is sensitive to high temperature. For the present study, we exploit those prior findings to address how the short-term induction of HSP gives way to the long-term maintenance of HSP at the NMJ. To do this, we have developed methods that combine *Drosophila* genetics with an hours-

long inhibition of *Drosophila* muscle glutamate receptors. In this way, we have been able to re-analyze previously characterized genetic manipulations that impair homeostatic signaling. The ultimate goal of this project is to organize homeostatic signaling molecules into coherent pathways and to provide temporal resolution to the processes that support both the induction and maintenance of homeostatic plasticity at the NMJ.

Disclosures: **K.M. Lembke:** None. **A.M. Spring:** None. **C. Frank:** None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.09/D50

Topic: B.07. Synaptic Plasticity

Title: Schizophrenia related protein Fxr1 controls homeostatic tuning of neuronal activity

Authors: ***J. KHLGHATYAN**¹, A. EVSTRATOVA², S. CHAMBERLAND³, A. MARAKHOVSKAIA², T. SOARES SILVA², V. MONGRAIN⁴, K. TOTH³, J.-M. BEAULIEU²
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Abstract: Background: Genetic variants of the fragile X mental retardation syndrome-related protein 1 (*FXR1*) are associated with mood regulation, schizophrenia, and bipolar disorders. Nonetheless, the genetic association does not indicate a functional link to neuronal activity and plasticity. Mental illnesses are believed to be associated to a miss-regulation of excitation/inhibition balance. Homeostatic scaling is a form of plasticity that tunes synaptic strength in response to environmental changes. Disruption in homeostatic plasticity could be one of the causes of imbalances of neuronal activity, thus it has been postulated to be implicated in mental illnesses. However, the contribution of genetic risk factors for schizophrenia and mood disorders to the regulation of homeostatic scaling in mammalian nervous systems remains elusive. **Methods:** We used CRISPR/Cas9 mediated knockout and overexpression to investigate the impact of Fxr1 and its negative regulator Gsk3 β on homeostatic plasticity in two different models: TTX induced multiplicative upscaling in primary neuronal cultures *in vitro* and sleep deprivation induced additive upscaling in mPFC *in vivo*. **Results:** We have discovered that TTX induced homeostatic synaptic upscaling in primary neuronal cultures is accompanied with an increase of synaptic GluA1 and a decrease in expression of Fxr1. Augmentation of Fxr1 expression was sufficient to completely abolish upscaling. Interestingly CRISPR/Cas9 mediated knockout of Gsk3 β , the negative regulator of Fxr1, also blocked upscaling. CRISPR/Cas9 mediated knockout of Fxr1 induced a multiplicative upscaling phenotype regardless of TTX treatment. This indicates that a decrease of Fxr1 expression is necessary and sufficient for homeostatic upscaling. We have identified that sleep deprivation induced increase in synaptic

strength, similarly to *in vitro* upscaling, is accompanied with an increase of synaptic GluA1 and a decrease in expression of Fxr1. Further analysis indicated that sleep deprivation induced changes of neuronal activity resemble the additive homeostatic upscaling phenotype. Moreover, similar to *in vitro* upscaling, additive upscaling was also abolished by augmentation of expression of Fxr1 and reduction of its negative regulator Gsk3 β . **Conclusions:** These results underscore a regulatory role of Fxr1 across different types of homeostatic regulation of neuronal activity *in vitro* and *in vivo*. The association between homeostatic plasticity and Fxr1 also suggests how it can contribute to neuronal plasticity in response to environmental conditions, such as sleep deprivation, and in illnesses like mood disorders and schizophrenia.

Disclosures: **J. Khlghatyan:** None. **A. Evstratova:** None. **S. Chamberland:** None. **A. Marakhovskaia:** None. **T. Soares Silva:** None. **V. Mongrain:** None. **K. Toth:** None. **J. Beaulieu:** None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.10/D51

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS091546

Title: Distinct neuronal subtypes and induction mechanisms drive acute and chronic homeostatic signaling

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Abstract: Homeostatic signaling mechanisms modulate presynaptic neurotransmitter release at synapses in diverse organisms ranging from invertebrates to humans. At the *Drosophila* neuromuscular junction, a highly conserved retrograde signaling system is activated following postsynaptic glutamate receptor perturbation that enhances presynaptic efficacy to maintain normal muscle excitation, a process termed Presynaptic Homeostatic Potentiation (PHP). We have recently demonstrated that disparate induction mechanisms in the postsynaptic cell drive PHP over both acute and chronic timescales with differential dependencies on gene translation and calcium signaling. Here, we present evidence for mechanistic differences between acute PHP, induced by pharmacological glutamate receptor blockade, compared to chronic PHP, induced by genetic loss of postsynaptic glutamate receptors. We find that chronic PHP is expressed at one of the two motor neuron subtypes (type Ib) innervating most muscles in *Drosophila*. However, quantal imaging reveals that acute PHP is induced and expressed at both type Ib and type Is motor neuron subtypes, demonstrating that type Is terminals are capable of

expressing PHP, but that glutamate receptor loss itself is insufficient to induce PHP signaling at type I terminals. Finally, we show evidence that a compartmentalized reduction in postsynaptic CaMKII activity is necessary for chronic PHP signaling, but is surprisingly dispensable for acute PHP expression. Thus, we consider an attractive model in which pharmacological disruption of glutamate receptor functionality induces PHP via intercellular, trans-synaptic signaling through receptor conformational changes at postsynaptic regions of both neuronal subtypes. In contrast, chronic PHP signaling requires compartmentalized changes in calcium signaling that occurs specifically at postsynaptic densities of type Ib terminals. The involvement of both motor neuron subtypes in acute PHP might ensure a robust and reliable mode of enhancing presynaptic release when acutely challenged with exogenous toxins.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.11/E1

Topic: B.07. Synaptic Plasticity

Support: ERC Advanced Grant 694829 'neuroXscales'

Title: Mechanisms of homeostatic synaptic plasticity

Authors: *J. BARTRAM, M. SCHRÖTER, S. RONCHI, V. EMMENEGGER, J. MÜLLER, A. HIERLEMANN
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Abstract: Homeostatic plasticity is a crucial set of mechanisms acting at typically slow temporal scales in order to stabilize neuronal spike rates. Despite the functional significance of such processes, revealing the precise induction mechanisms has proven to be difficult, as the roles of postsynaptic spiking and synaptic activity are still debated. For a clearer picture of the induction process to emerge, information about synaptic efficacies of multiple inputs needs to be combined with accurate information about spiking activities of the respective presynaptic cells and the postsynaptic cell during the induction of homeostatic plasticity. In this study, we were able to achieve such measurements by performing combined high-density microelectrode array (HD-MEA) and whole-cell patch-clamp recordings in cultures of primary cortical neurons. Homeostatic plasticity was induced by pharmacological alteration of global network spiking and synaptic transmission with TTX or CNQX. Monosynaptic connections between neurons - here with a focus on excitatory connections between pyramidal cells - were identified by correlating presynaptic spiking activity (HD-MEA recordings) with postsynaptic subthreshold responses

(patch current-clamp recordings). Presynaptic spiking was spontaneously observed or could be induced via the stimulation capabilities of the HD-MEA system. This experimental approach enabled us to link changes in synaptic efficacy with the respective pre- and postsynaptic spike patterns, recorded during the induction phase, which sheds new light on the rules and mechanisms of homeostatic synaptic plasticity at excitatory synapses.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

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Program #/Poster #: 037.12/E2

Topic: B.07. Synaptic Plasticity

Support: PAPIIT IN215816
CONACYT 478912

Title: Conditioned taste aversion disrupts the induction of neocortical long-term depression *in vivo*

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Abstract: Metaplasticity is a homeostatic process by which neurons modulate their synaptic strength depending on their previous history of activity. Accumulated evidence has proposed that metaplasticity contributes to network function and cognitive processes such as learning and memory. Accordingly, it has been observed that training in several behavioral tasks modifies the possibility to induce subsequent synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD). In this regard, our previous studies have shown that conditioned taste aversion (CTA) training prevents the induction of LTP in the projection from the basolateral nucleus of the amygdala to the insular cortex (BLA-IC). Likewise, we have also reported that extinction of CTA allows induction but not maintenance of LTP in the same pathway. In this order of ideas, LTD is thought to be essential for memory extinction. However, its participation on metaplastic processes is still poorly understood. Related to this, a recent study from our group showed that induction of LTD in the BLA-IC projection before CTA training facilitates the extinction of this task. The aim of the present study was to analyze whether CTA training modifies the expression of *in vivo* LTD in the BLA-IC projection. Thus, 48 h after CTA

training animals received low frequency stimulation in order to induce IC-LTD. Our results show that CTA training prevents the subsequent induction of LTD in the BLA-IC pathway. These findings reveal that CTA elicits a metaplastic regulation of long-lasting changes in IC synaptic strength.

Disclosures: E. Urrieta: None. M.L. Escobar: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.13/E3

Topic: B.07. Synaptic Plasticity

Title: Effects of methylphenidate and amphetamine on glutamatergic neurons from nucleus accumbens

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Abstract: Synaptic changes in nucleus accumbens (NAc) underlie drug addiction, most of NAc neurons are GABA neurons, that receive glutamate inputs from cortical and limbic nuclei for regulating motivated behaviors, including drug seeking, and activate motor regions important for the execution of motivated behaviors. Several studies indicate that AMPA transmission in both core and shell can play a role in drug seeking. Cocaine and amphetamine (AMPH) exhibit cross-sensitization in locomotor activity experiments and prior exposure to one drug enhances self-administration of the other. Methylphenidate (MPD) and AMPH are similar in terms of their actions at the dopamine (DA) transporter. Since these two drugs produce comparable increases in synaptic DA levels and produce similar behavioral effects, it is possible that both drugs share the same modulatory effects on AMPA transmission on Nucleus accumbens. The present study analyzes the effect of MPD and AMPH on the glutamatergic synaptic transmission on NAc neurons. Animals were treated according to the SfN's Policies on the Use of Animals and Humans in Neuroscience Research. Brain slices were obtained from 3-8 week old Wistar male rats anaesthetized with diethyl ether and decapitated. Coronal brain slices (350-400 μm thick) containing the NAc were sectioned by a Vibratome. Slices preparation and recordings were made using standard methods and procedures. The location of the recorded neurons was visualized by a stereo microscope, using the anterior commissure, neostriatum, septum and lateral ventricles as landmarks based on a rat brain atlas. Data acquisition was performed with pClamp 7.0, and analysis was performed with Clampfit. Visualized whole-cell voltage-clamp recording was performed using electrodes, with a resistance 3-4M Ω , Cells were voltage clamped at -70 or +40 mV. Single or paired pulses (0.2- 0.5 ms) were delivered every 2 min to evoke excitatory

postsynaptic currents (EPSCs). AMPA-mediated EPSCs were recorded when holding cells at -70 mV in the presence of a NMDA receptor antagonist. NMDA-mediated EPSCs were calculated by subtracting the EPSCs recorded at +40 mV before and after adding the NMDA antagonist. AMPA/NMDA ratios were calculated by dividing the AMPA-mediated EPSCs to the NMDA-mediated EPSCs. AMPA and NMDA receptor-mediated EPSCs were inhibited by the addition of MPD and AMPH, suggesting a presynaptic mechanism of action. However the effects of MPD on NMDA transmission were more significant than those induced on AMPA, contrarily, AMPH exerts a more important effect on AMPA than on NMDA transmission. These findings show that acute MPD and AMPH modulate differently the glutamatergic transmission in NAc.

Disclosures: A. Vazquez-alvarez: None. D. Pineda-vazquez: None. B. Prieto-Gómez: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

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Program #/Poster #: 037.14/E4

Topic: B.07. Synaptic Plasticity

Support: CONACYT CB 2013-221653 to MA

Title: Social Defeat-induced Interleukin 6-dependent synaptic changes in the prefrontal cortex of the mouse

Authors: *M. MIRANDA-MORALES¹, E. ESQUIVEL-RENDÓN¹, J. VARGAS-MIRELES¹, P. ACOSTA-MARES¹, R. CUEVAS-OLGUÍN¹, S. ROSE-JOHN², M. ATZORI¹

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Abstract: Social stress is an important trigger for neuropsychiatric disease. The medial prefrontal cortex (mPFC) is a brain area critically involved in decision making especially sensitive to social stress. The pro-inflammatory cytokine interleukin 6 (IL-6) has been positively correlated with the onset of numerous stress-triggered neuropsychiatric conditions including schizophrenic psychoses and depression. This study sought to identify synaptic alterations induced by social stress in the prefrontal cortex, and whether IL-6 trans-signaling is involved in any such type of plasticity. To this purpose we compared synaptic properties of a group of wild type animals (WT) with those of genetically modified mice in which IL-6 central trans-signaling was blocked by overexpression of the IL-6 transducer glycoprotein 130 in astrocytes (GFAP-sgp130Fc, TG). C57BL/6 mice were submitted to a well-established chronic Social Defeat (SD) protocol, consistent in a 10 min exposure to different preselected aggressive CD1 mouse every day during 10 days. Four experimental groups were used for the experiments: control and SD-exposed WT mice, and control and SD-exposed TG mice. SD-exposed animals were further

divided into SD-resilient (R) and SD-sensitive mice (S), according to their response to a peculiar version of the Open Field test. Our results showed that SD greatly reduces the ratio between N-methyl D aspartate receptor dependent vs. the amino propionic acid receptor dependent currents (I_{NMDA}/I_{AMPA}) whereas it decreases the ratio between I_{AMPA} and the gamma amino butyric acid receptor dependent current (I_{AMPA}/I_{GABA}) in an IL-6 dependent manner selectively in R or S animals, respectively. SD also reduced the frequency but not the amplitude of both excitatory and inhibitory action-potential independent synaptic currents, and increased almost threefold the frequency of action-potential dependent spontaneous excitatory currents selectively in S mice while decreasing their amplitude, also in a IL-6 dependent manner. Our results indicate that IL-6 may be critical in the induction of synaptic plasticity both in SD-resilience and SD-sensitivity, corroborating the relevance of this cytokine in the effects of stress in the mPFC.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

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Program #/Poster #: 037.15/E5

Topic: B.07. Synaptic Plasticity

Support: Conacyt, CB221653 to MA

Title: The proinflammatory cytokine interleukin 6 is involved in behavioral and synaptic changes induced by prolonged exposure to continuous illumination

Authors: *M. MORQUECHO ROBLEDO¹, R. D. CUEVAS-OLGUIN³, M. MIRANDA-MORALES², R. VELAZQUEZ-CONTRERAS³, F. VEGA³, J. VARGAS-MIRELES³, C. ARENAS-HUERTERO³, N. SADERI³, R. C. SALGADO⁴, S. ROSE-JOHN⁵, M. ATZORI⁶
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Abstract: The proinflammatory cytokine interleukin 6 (IL-6) is involved in the effects of numerous types of stress. Since all mammals -as most biological living beings- are naturally synchronized to circadian rhythms, through a neural circuitry built-in to the limbic system. Artificial alterations of such daily oscillations have the potential to produce important biological distressing effects. We wondered whether IL-6 is involved in the biological effects associated

with the loss of circadian rhythms caused by prolonged exposure to continuous illumination. To answer this question we used a protocol of 6-week continuous illumination (L:L, vs. normal illumination, L:D) and compared behavioral and synaptic effects on wild type (C57BL/6, WT) mice vs. genetically modified mice in which IL-6 central trans-signaling was blocked by overexpression of the IL-6 transducer glycoprotein 130 (GFAP-sgp130Fc, TG). Porsolt forced swimming test (PFSR) was used after 3 or 4 week from the start of the protocol, to assess behavioral effects while patch-clamp recording from prefrontal cortex layer 5 was used to monitor the properties of synaptic transmission of four groups of animals: WT L:D, WT L:L, TG L:D, and TG L:L. While the PFWT was effective in increasing the percentage of immobility time (%IT) in all groups after 4 week, TG animals displayed lower %IT after 3 weeks, suggesting that central IL-6 may be involved in the induction of the behavioral consequences of continuous illumination. Excitatory and inhibitory action-potential independent postsynaptic currents (mEPSC and mIPSC, respectively) were recorded in the presence of a Na⁺-channel blocker. While mEPSC frequency and amplitude, as well as mIPSC frequency did not differ between TG and WT, mIPSC amplitude was significantly lower in L:L vs. L:D, only in WT but not in TG animals. Kinetic mIPSC analysis showed likewise that the 50% amplitude time width was significantly faster in L:L vs. L:D, but only in WT and not in TG animals, suggesting that disruption of circadian rhythm alters inhibitory synaptic function, and corroborating the possibility that IL-6 is involved in central changes induced by constant illumination.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.16/E6

Topic: B.07. Synaptic Plasticity

Title: Primed suppressive paired associative stimulation

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Abstract: Purpose: Paired associative stimulation (PAS) alters neuroplasticity by pairing peripheral nerve and cortical stimuli, which induces spike-timing-dependent-like plasticity. Preceding a principal bout of PAS that intends to weight plasticity in one direction (e.g. suppressive or PAS_{LTD}) with a priming bout of PAS that intends to weight plasticity in the

opposite direction (e.g. facilitatory or PAS_{LTP}) may deploy homeostatic synaptic mechanisms resulting in a greater change from baseline corticospinal excitability in the desired, principal, direction. This study explores the efficacy of primed suppressive PAS as a method of neuromodulation and investigates a relationship between individual characteristics and response to PAS. **Methods:** Fifteen healthy individuals (age 23.60 ± 2.33 years) completed a cross-over study of the following four primed interventions separated by at least one-week washouts: 1. PAS_{SHAM}→PAS_{LTD}; 2. PAS_{LTP}→PAS_{LTD}; 3. PAS_{LTD}→PAS_{LTD}; 4. PAS_{SHAM}→PAS_{SHAM}. The primary outcome was the average peak-to-peak amplitude of 20 motor evoked potentials (MEPs) recorded at baseline and 0, 10, 20, 30, 40, 50 and 60 minutes following intervention. Data analyses used a mixed linear model. The secondary predictor was presence of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism. **Results:** The PAS_{LTP}→PAS_{LTD} intervention produced a significant *increase* (average 30.4% with 95% CI 5.4%, 61.2%, $p=0.015$) from baseline corticospinal excitability, opposite to the hypothesis that this combination would create a significant *decrease* in excitability. Significantly more non-responders than responders had the BDNF Val66Met polymorphism. **Discussion:** The paradoxical response following PAS_{LTP}→PAS_{LTD} highlights the complexity of synaptic plasticity and may reveal another method of significantly increasing corticospinal excitability. Presence of the BDNF Val6Met polymorphism may influence an individual's response to PAS_{LTD}.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.17/E7

Topic: B.07. Synaptic Plasticity

Title: Period1-dependent molecular mechanisms behind daytime-dependent plasticity in mouse hippocampus

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Abstract: The ability to convert transient stimuli into long-term changes of brain function is central to the capacity of an animal to adapt to a dynamic environment by learning. In mouse, hippocampus integrity ensures proper memory acquisition, consolidation, and retrieval. Notably, hippocampus-specific cellular and molecular dynamics that are associated with long-term memory (LTM) formation are clearly molded by time-of-day and depend on proper output from

the master circadian (*circa*: about; *dies*: day) clock in the suprachiasmatic nucleus. Here it is initially confirmed that mice perform better in a food-rewarded spatial memory task during daytime, thus, their resting period. In parallel, the time-of-day-dependent LTM formation is tightly coupled to post-translational modifications and/or de novo gene expression of plasticity-related proteins, relies on intact cAMP/PKA/PKC/CREB signaling and requires chromatin remodeling. In addition, compelling evidence suggests that hippocampus-dependent LTM formation is mirrored in the plasticity of long-term potentiation (LTP) efficiency, structural synaptic plasticity, synaptic excitability and the responsiveness to synaptic input follow a similarly clear time-of-day dependency as molecular events. Notably, all observed rhythms including daytime-dependent learning efficiency depend on a dynamic expression of the clock gene PER1 in mouse hippocampus. These observations argue for an intricate interplay between the circadian system and memory. Mechanistically, we reveal a PER1-dependent modulation of cytoplasmic-to-nuclear trafficking of the CREB kinase pPRSK90 in murine hippocampal cells. Co-immunoprecipitation assay confirmed a high affinity interaction between PER1 and bpP90RSK. Taken together, our data provide a molecular explanation for how the circadian system potentially shapes a temporal framework for memory performance dependent on time-of-day, and adds a novel facet to the versatility of the clock gene protein PER1.

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Poster

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Program #/Poster #: 037.18/E8

Topic: B.07. Synaptic Plasticity

Support: 5R25NS080687
2R25GM061151-13
1156810

Title: Pumilio, a possible link between sleep and neuronal homeostasis

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Abstract: Sleep disorders and mental conditions that provoke chronic sleep deprivation correlate to higher risk of neuronal and mental disorders. Previous findings have shown that acute sleep deprivation (12-24 hours) is associated with a widespread increase in the expression of synaptic proteins such as Brp (Bruchpilot), a drosophila presynaptic protein with homology to the human protein CAST. This protein increase could implicate a relationship between neuronal homeostasis and sleep homeostasis. However, this increase in synaptic proteins has yet to be seen on a chronic level of sleep deprivation, and not much is known about the regulatory mechanisms involved. Evidence from our laboratory have shown that when the homeostatic, neuronal regulator Pumilio is knockdown, there is a lack of homeostatic sleep. Using immunohistochemistry for Brp, we studied the effect that chronic deprivation and a knockdown of Pumilio within the neuronal circuit of circadian regulation(tim-gal4) has on the expression of synaptic proteins. Preliminary results show a widespread reduction of Brp staining as a consequence of chronic deprivation. The knockdown of pumilio in the tim-gal4 circuit lowers overall Brp staining. This seems to indicate that chronic sleep deprivation activates a homeostatic regulation not present during acute deprivation, and that pumilio is necessary to achieve that regulation.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 037.19/E9

Topic: B.07. Synaptic Plasticity

Title: PVN:CRH neurons anticipate innate defensive behaviors

Authors: *N. DAVIU, T. FUZESI, D. ROSENEGGER, N. RASIAH, T.-L. STERLEY, J. S. BAINS

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Abstract: Threat motivates animals to deploy innate and learned defensive behaviors to ensure survival. The response can be modified by a prior stressful experience, but how this occurs, is not known. Here we identify CRH neurons in the paraventricular nucleus of the hypothalamus (PVN) as essential hubs for linking prior stress to behavioral strategies in unrelated situations. Monitoring deep brain calcium dynamics revealed that CRH neurons anticipate active (escape) but not passive (freeze) responses to a looming visual threat. Optogenetic silencing of these cells decreased escape, positioning PVN CRH neurons as integral components of the active response to a visual threat. We modified the anticipatory CRH response through training using cue-shock pairing with different contingencies. Training that allowed for learned escape in response to cue

(controllable stress) enhanced anticipatory activity in PVN:CRH neurons; meanwhile no anticipatory response was evident when cue-shock was uncoupled from a behavioral response (uncontrollable stress). The anticipatory response was a strong predictor of subsequent defensive behavior in response to a visual threat. These findings demonstrate that stress controllability changes the anticipatory response of PVN CRH neurons to threat resulting in a trans-situational shift in the balance between active and passive defensive behaviors.

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Poster

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Topic: B.07. Synaptic Plasticity

Support: NINDS F32NS101832
NINDS R37NS092635
NINDS P01NS079419

Title: Labeling of cortical neurons based on their baseline firing rate in freely behaving mice

Authors: *N. TROJANOWSKI¹, B. MOEYAERT², E. R. SCHREITER², G. TURRIGIANO¹
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Abstract: Chronic electrode recordings have revealed that in response to prolonged monocular deprivation, the mean firing rate of pyramidal neurons in the visual cortex initially decreases before homeostatically rebounding. Remarkably, although the baseline firing rates of these neurons are lognormally distributed across multiple orders of magnitude, the firing rates of individual neurons return to close to their original value following a perturbation, demonstrating that these neurons have intrinsic firing rate set points. This broad range of baseline firing rates has been seen in a variety of organisms and across different regions of the central and peripheral nervous system. However, the factors that determine where any individual neuron sits within this range are unknown. Fluorescent reporters of immediate early gene (IEG) activity, such as arcGFP and fosGFP, have been used to compare the electrophysiological properties of neurons with and without IEG expression but the relationship between firing rate and IEG expression has not been established, and the molecular, structural, or anatomical determinants of disparate firing rates within a particular cortical cell types are unknown.

To identify neurons with different baseline firing rates in freely behaving mice, we used the photoconvertible activity marker CaMPARI2, which converts from green to red in the presence

of UV light and Ca²⁺. After illuminating a region of visual cortex for 30 minutes at low light intensity, we observed neurons with a wide range of green-to-red photoconversion (PC) ratios. To verify that the neurons with a higher degree of PC are the same as those with higher firing rates *in vivo*, we measured the firing rates and PC ratios of pairs of nearby neurons in active acute slices. We found that in almost all cases, the neuron with a higher firing rate also showed a greater degree of PC *in vivo*. Further, we found a moderate overlap between cFos expression and PC ratio, highlighting the need for an IEG-independent approach for measuring baseline firing rates. These data demonstrate our ability to identify and differentiate neurons with different baseline activity levels and set the stage for future exploration of the electrophysiological, molecular, and anatomical differences between neurons with different firing rate set points.

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Poster

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Topic: B.07. Synaptic Plasticity

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NWO VIDI #91712361

Title: Dendritic coordination between excitatory and inhibitory synapses via endocannabinoid signalling

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Abstract: Balanced excitatory and inhibitory synaptic inputs within dendrites are essential for proper functioning of individual neurons. As inhibitory synapses are most efficient in inhibiting excitatory inputs localized on the same dendrite, their formation and plasticity may be coordinated locally. Here, we explore whether excitatory and inhibitory inputs are coordinated within dendrites. We used two-photon microscopy to visualize crossings between dendrites of CA1 pyramidal cells (labeled via patch pipette) and GFP-labeled GABAergic axons in organotypic hippocampal slice cultures of GAD65-GFP mice (of both sexes, dissected at P6-7, used at DIV10-21). We stimulated four dendritic spines close (less than 10 µm) to the inhibitory axon crossing by pairing repeated two-photon glutamate uncaging (30x @0.5Hz) with postsynaptic somatic depolarization (0 mV, 100 msec) to induce excitatory potentiation. We observed that this spine stimulation protocol often induced growth of an inhibitory presynaptic

bouton on the nearby axon-dendrite crossing. Spine stimulation increased the probability of inhibitory bouton growth from 11% (3/27 experiments) to 27% (9/34 experiments). Inhibitory bouton growth was blocked by application of the N-methyl-D-aspartate receptor (NMDAR) antagonist APV. However, inhibitory bouton growth did not occur when spines were stimulated in low Mg^{2+} artificial cerebrospinal fluid (ACSF) in absence of postsynaptic depolarization, suggesting that NMDA receptor activation is necessary, but not sufficient, to induce inhibitory bouton growth. Glutamate uncaging near the inhibitory axon did not induce growth events, indicating that the postsynaptic dendrite was necessary for triggering inhibitory bouton growth, suggesting a possible role for retrograde messengers. Local application of the endocannabinoid 2-arachidonoylglycerol (2-AG), but not brain-derived neurotrophic factor (BDNF), on inhibitory axons lead to an increase in inhibitory bouton growth, suggesting that endocannabinoids may be involved in this process as a retrograde messenger. Indeed, the spine stimulation protocol failed to induce inhibitory bouton growth in presence of the cannabinoid receptor type 1 (CB1R)-antagonist AM251. Our findings show that endocannabinoids act as a heterosynaptic retrograde signaling messenger in dendrites to coordinate excitatory and inhibitory synapses.

Disclosures: D.L.H. Kruijssen: None. H.Y. Hu: None. B. Rózsa: None. C.C. Hoogenraad: None. C.J. Wierenga: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

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Program #/Poster #: 037.22/E12

Topic: B.07. Synaptic Plasticity

Support: 2015R1D1A1A02059430

Title: Salt loading enhances Mg^{2+} resistive tonic NMDA current in supraoptic nucleus

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Abstract: The hypothalamic supraoptic nucleus (SON) contain magnocellular neurosecretory cells (MNCs): consist of vasopressin (VP) and oxytocin (OT) which synthesize and release neuropeptide vasopressin and oxytocin hormone respectively. Vasopressin play important role in homeostatic by reuptake of water from kidney and regulate blood pressure while oxytocin has role in reproduction including delivery at birth and breastfeeding. Similar with other brain region glutamate is the major excitatory amino acid in hypothalamus preferentially binds with glutamate receptor to regulate excitability of SON MNCs. Among the ionotropic glutamate receptors, NMDA is the most abundant receptors, which maintain synaptic plasticity in MNCs. NMDA receptor has characteristics of burst firing which is proportional to hormone release from cells. In

this study, we investigated that 7 days salt loading (SL) enhances the tonic NMDA current in SON. In low Mg^{2+} artificial cerebrospinal fluid (aCSF) almost half of SON MNCs from SL C57BL/6(WT) shows enhanced tonic NMDA current which is sensitive to the NR2C/2D subunit selective antagonist; PPDA and enhanced current was consistent in normal aCSF too; this suggest SL enhances Mg^{2+} resistive tonic NMDA current in SL MNCs . Similarly, half of SL SON MNCs from WT has PPDA sensitive firing inhibition suggest increased neuronal firing in salt loading. Genetically knockdown of the NR2D fails to show Mg^{2+} resistive tonic NMDA current and neuronal firing inhibition by PPDA in SL MNCs. Cell type specific recording from SL VP transgenic (eGFP) and OT transgenic (eRFP) rats shows that tonic NMDA current was enhanced only in SL VP neurons not in OT neurons and EU MNCs. With the neuronal firing only SL VP neurons shows the PPDA sensitive firing inhibition. Collectively our study suggest that SL VP neurons enhances Mg^{2+} resistive tonic NMDA current mediated by NR2D subunits containing receptors that regulate the homeostasis in the chronic osmotic challenge.

Keywords: Salt loading; vasopressin; oxytocin; NMDA receptor; supraoptic nucleus

Disclosures: C. Neupane: None. R. Sharma: None. J. Park: None.

Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

Location: SDCC Halls B-H

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Program #/Poster #: 037.23/E13

Topic: B.07. Synaptic Plasticity

Support: PAPIIT IN215816

Title: Extinction of conditioned taste aversion prevents the maintenance of *in vivo* insular cortex LTP through calcineurin participation: A metaplastic effect

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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. Some studies have proposed that synaptic potentiation evoked by learning are dampened after extinction. In this regard, it has been proposed to depotentiation of excitatory synapses as a cellular mechanism for memory extinction. On the other hand, it is considered that synaptic strength is homeostatically regulated in order to maintain the circuit stability that is crucial for memory storage. In this order of ideas, training in several behavioral tasks modifies the possibility to induce long-term potentiation (LTP). Our previous studies have shown that

prior training in conditioned taste aversion (CTA) prevents the subsequent induction of LTP in the projection from the basolateral nucleus of the amygdala (Bla) to the insular cortex (IC) in vivo. Additionally, we recently reported that induction of LTP in the Bla-IC pathway increases the retention of CTA while LTD induction facilitates its extinction. Accordingly, the direction of synaptic change is delicately controlled by the level and pattern of calcium increases and the associated activation of protein kinases and phosphatases. In this sense, a body of evidence suggests that protein phosphatase calcineurin (CaN) is involved in the extinction of some behavioral tasks. The aim of the present study was to analyze the effect of CTA extinction on the ability to induce subsequent LTP in the BLA-IC projection in vivo, as well as, the potential role of CaN in this process. Thus, 48 h after CTA extinction animals received high frequency stimulation in order to induce IC-LTP. Our results show that extinction training allows the induction but not the maintenance of IC-LTP as well as increases the CaN expression in the IC. Likewise, the inhibition of this phosphatase was able to revert the effect of CTA-extinction on the IC-LTP. These findings reveal that CTA extinction promotes a homeostatic regulation of subsequent IC synaptic plasticity maintenance through increases in CaN levels.

Disclosures: **J. Nelson-Mora:** None. **M. Gonsebatt:** None. **M.L. Escobar:** None.

Poster

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Program #/Poster #: 037.24/E14

Topic: B.07. Synaptic Plasticity

Support: PAPIIT-DGAPA-UNAM-IN216214
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Title: Neuropeptide vasopressin may have synapse organizing functions in multiple limbic regions throughout the brain

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Abstract: The synapse is a nano-organized membrane specialization which involves the presynaptic bouton and postsynaptic membranes, whether a segment of dendrite or soma. The synapse undergoes dynamic/plastic changes in short- and long- time scales, which is the cellular basis of learning and memory. The strengthening and weakening of synapses require adaptive changes of their components. In the 1970s, some synapses were found to release a peptide co-transmitter that can modify the action of the classic, small-molecule. However, this phenomenon

has been largely overlooked in the last four decades since very few ultrastructural (at electron microscopy level) evidence were reported. Using immuno-electronmicroscopic methods, we have documented that large diameter axon terminals coming from hypothalamic magnocellular vasopressin system, (immunopositive to AVP) are fairly often observed that large dense core vesicles (LDCV), in co-storage in the active zone, adjacent to the presynaptic membranes, in limbic regions such as hippocampus, amygdala and lateral habenula. Some of those LDCV seemed to be docked onto the presynaptic membrane. To further address this question we performed Western blots for major post-synaptic-density (PSD) protein levels, PSD-95, GKAP, SAP97, ERK, GluR1, latrophilin 2 and 3, and tubulin, at several time points, in rats and mice under osmotic stress, using the experimental model of 48 hrs. water deprivation (WD-48). With this physiological measure, the hypothalamic vasopressin system is up-regulated in a relatively selective manner, even before a significant disruption of the body's water homeostasis occurs. Preliminary results showed significant increases in PSD95 protein levels in medial division of the lateral habenula, central amygdala and CA2-CA3 regions of the ventral hippocampus in the time points WD-48 and 24hr post WD, compared with the basal level. Our findings provide a structural basis for further understanding the regulatory role of the neuropeptide vasopressin for synaptic plasticity.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

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Topic: B.07. Synaptic Plasticity

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Title: Cyclophilin D regulates neuronal activity-induced filopodiogenesis by fine-tuning dendritic mitochondrial calcium dynamics

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Abstract: Mitochondria play a pivotal role in maintaining intra-neuronal calcium homeostasis. Recent studies have highlighted the critical function of mitochondria in supporting dendritic spinogenesis. Such function is closely associated with mitochondrial energy provision and calcium handling. Cyclophilin D (CypD, gene name: *Ppif*) is a mitochondrial peptidyl-prolyl cis-trans isomerase (PPIase) located in mitochondrial matrix, which controls the opening of mitochondrial permeability transition pore (mPTP). Of note, transient CypD-mediated mPTP is an essential physiological event that controls mitochondrial calcium retention. In this regard, we sought to examine whether transient CypD-mediated mPTP involves in the regulation of neuronal activity-induced dendritic spine outgrowth. Our results showed that genetic CypD depletion results in compromised dendritic spinogenesis, in particular the outgrowth of filopodia in response to KCl-mediated neuronal depolarization. Along with the above changes, CypD-deficient neurons exhibited a faster clearance of intra-dendritic calcium and greater mitochondrial calcium retention in response to KCl stimulation as compared with their wildtype counterparts. Moreover, CypD deficiency conferred resistance to calcium-related CamkII activation as well as dendritic mitochondrial motility change against KCl-induced neuronal depolarization. Of note, there was no significant difference in mitochondrial calcium uniporter (MCU) or mitochondrial sodium-calcium exchanger (mHCX) between mitochondria in the two genotypes of cultures, further implicating the critical role of CypD-mediated transient mitochondrial calcium release in the formation of dendritic protrusions during neuronal activity. Intriguingly, we have also seen a significant protection of loss of CypD on dendritic mitochondria and dendritic protrusions against oxidative stress. Interestingly, loss of CypD attenuates oxidative stress-induced mitochondrial calcium perturbations and dendritic protrusion injury, implying the benefits of CypD inhibition to neuronal physiology in pathological conditions. In summary, our study has revealed the physiological function of CypD in dendritic plasticity by acting as a fine-tuner of mitochondrial calcium homeostasis. Moreover, CypD plays distinct roles in neuronal physiology and pathology, which raises concern on CypD inhibition for disease prevention.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

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Topic: B.07. Synaptic Plasticity

Support: NIH Intramural Research Program (IRP)

Title: Tuning dendritic plasticity by modulating nicotinic acetylcholine receptor expression and trafficking

Authors: *J. S. ROSENTHAL^{1,2}, J. YIN³, C. LONG³, Q. YUAN³

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Abstract: During nervous system development, the intrinsic developmental program interacts with changing external inputs, which generate modifications to ensure proper establishment of circuit connectivity. Using the *Drosophila* model, we have built a formidable understanding of the mechanisms of synapse formation as well as its modulation in response to neural activity. However, previous studies focused on glutamatergic synapses at the Neuromuscular Junction (NMJ) and much less is known about the formation and regulation of cholinergic synapses, which are the main excitatory synapses in the *Drosophila* central nervous system (CNS). Here, we analyze activity-dependent modification of cholinergic synapses in ventral Lateral Neurons (LNvs) of the *Drosophila* larval visual circuit. LNvs receive cholinergic inputs from presynaptic photoreceptors and exhibit experience-dependent homeostatic structural plasticity *via* robust changes in dendrite volume during development. Specifically, chronically elevated activity (LL) reduces the dendritic size of LNvs, which are also less responsive physiologically as demonstrated by calcium imaging.

Using LNv-specific transcriptome analysis followed by *in vivo* transgenic RNAi screens, we isolated candidate molecules that potentially contribute to LNv plasticity. Among them were two genes encoding nicotinic acetylcholine receptors subunits, nAChR α 1 and nAChR α 6, both of which exhibit activity-modified transcription profiles in LNvs. We first confirmed their expression in LNvs using Trojan-Gal4 lines generated by MiMIC insertions in nAChR α 1 and nAChR α 6 coding regions. Next, using cell-specific RNAi knockdown in the LNvs, we observed that deficiencies in these receptors result in dendritic arbor volumes which are invariable between light conditions, suggesting that these subunits may be an integral part of the plasticity mechanism. Morphological analysis using a null nAChR α 6 allele confirmed this finding. To understand the link between neuronal activity and the transcriptional regulation of nAChRs, we performed bioinformatic analysis and expression studies, which revealed a potential role for the transcription factor *fruitless* in mediating activity-induced modification of nAChRs and dendrite plasticity. Taken together, our work identified specific nAChR subunits that regulate the structural plasticity in the *Drosophila* central synapse and revealed the role of activity-dependent transcriptional regulation in tuning neurotransmitter signaling during development.

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Poster

037. Synaptic Plasticity: Homeostatic Plasticity I

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Program #/Poster #: 037.27/E17

Topic: B.07. Synaptic Plasticity

Support: SFB 1149

Title: Modulation of synaptic plasticity after thorax trauma

Authors: *S. CURSANO¹, C. BATTAGLIA¹, S. GRABRUCKER², M. SCHOEN¹, A. M. GRABRUCKER², M. HUBER-LANG³, T. M. BOECKERS¹

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Abstract: Trauma is the leading cause of death, morbidity, hospitalization and disability in Americans from the age of 1 year to the middle of the fifth decade of life. As such, it constitutes a major health care problem. According to the Centers for Disease Control and Prevention, 130,557 deaths occurred from unintentional injury in 2013. In particular, chest trauma is a significant source of morbidity and mortality worldwide.

Trauma research has resulted in clear evidences on the pathophysiology after thoracic trauma, but in contrast, little is known about the effect of a peripheral trauma on the brain. In this context, the aim of this project is to analyze if a trauma of the periphery (i.e. of the thorax) results in alterations within the central nervous system especially focusing on the structure and a molecular organization of *spines*, *PSDs* and the *presynaptic active zone*.

To challenge this hypothesis, we made use of a well-established chest trauma mouse model at Ulm University. At different time intervals after trauma (5 days, 10 days, 18 days), we dissected the brain areas of the animals and subsequently analyzed them with respect to degeneration and regeneration of neurons and synaptic contacts. The main analyzed brain region has been the hippocampus, considering its central role in several neurodegenerative diseases. First, we closely analyzed the spine morphology by Golgi staining and the spine density in the hippocampus (CA1-CA3 subregions). Here, we found a significant decrease of spines of excitatory neurons after trauma and, interestingly, an almost full recovery after 18 days.

The hippocampus is part of the limbic system, the region that regulates emotions. It is associated mainly with memory, in particular long-term memory and it also plays an essential role in spatial navigation. Alterations in the hippocampus can lead to loss of memory and difficulty in establishing new memories. Since a delirium like state is often seen in patients after trauma we are now interested in analyzing whether synaptic loss after trauma is leading to a transitional impaired memory formation in mice.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 038.01/E18

Topic: B.07. Synaptic Plasticity

Support: NIH grant MH086403
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Title: Synaptic retinoic acid signaling mediates mTOR-dependent metaplasticity that controls hippocampal learning

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Abstract: Decades ago, non-Hebbian homeostatic synaptic plasticity was proposed as a major mechanism that prevents runaway Hebbian plasticity. However, whether impairing homeostatic synaptic plasticity actually predisposes to runaway Hebbian plasticity and produces negative behavioral consequences has never been tested directly. In mature mice, retinoic acid performs a well-established, non-genomic, and essential function in homeostatic synaptic plasticity. Here, we show that an enriched sensorimotor experience engages homeostatic RA signaling to control synaptic strength and contextual learning. Specifically, mice with a conditional deletion of RAR α in hippocampal CA1 neurons (CA1-RAR α KO) that exhibit impaired retinoic acid-dependent homeostatic plasticity, when placed in an enriched environment, exhibited greater long-term potentiation (LTP) and less long-term depression (LTD) than control mice; these changes were accompanied by improved hippocampus-dependent memory but strikingly reduced learning flexibility. Under the same conditions, mTOR activation and synthesis of AMPA receptors were enhanced, thus facilitating LTP expression. Rapamycin treatment that inhibits mTOR reversed runaway LTP and restored fear memory to normal levels in CA1-RAR α KO mice maintained in an enriched environment. Thus, our findings reveal a novel, RA-dependent synaptic mechanism by which homeostatic plasticity controls Hebbian plasticity and learning.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.02/E19

Topic: B.07. Synaptic Plasticity

Support: HD084215

MH086403

MH091193

Title: Direct interaction between FMRP and retinoic acid receptor alpha is critical for retinoic acid-mediated homeostatic plasticity

Authors: *L. CHEN, A. G. LAU, K. L. ARENDT

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Abstract: Retinoic acid (RA) is a morphogen known to play important roles in neurogenesis and neuronal development. Previous work from our lab has linked RA signaling through binding to the retinoic acid receptor alpha (RAR α) to changes in synaptic strength. RAR α , traditionally thought of as a transcription factor, binds to and represses the translation of specific mRNAs. The binding of RA to RAR α triggers dendritic protein synthesis and leads to concomitant up-regulation of excitatory synaptic strength and down-regulation of inhibitory synaptic strength, which, in the context of homeostatic synaptic plasticity, restores synaptic E/I balance and network activity. Another RNA-binding protein, the Fragile-X mental retardation protein (FMRP), is an important factor in RA-mediated homeostatic plasticity. Loss of FMRP, which results in Fragile X Syndrome (FXS), the most common form of inherited intellectual disability, abolishes RA-mediated homeostatic plasticity. However, the connection between FMRP and synaptic RA signaling through RAR α remains unknown. Here we show that FMRP and RAR α interact directly and the interaction is enhanced in the presence of RA. Loss of FMRP results in changes in the subcellular localization of RAR α in hippocampal neurons. Blocking the interaction between FMRP and RAR α with a small peptide, which corresponds to the critical binding site in RAR α , abolishes RA-induced increases in miniature excitatory postsynaptic current (mEPSC), recapitulating the phenotype seen in the neurons from *Fmr1* knockout mouse and human neurons derived from FXS patients. Taken together, these data suggest that the interaction between FMRP and RAR α is essential for proper non-genomic RA signaling, which provides further mechanistic insight into FXS pathophysiology.

Disclosures: L. Chen: None. A.G. Lau: None. K.L. Arendt: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Title: Retinoic acid-dependent synaptic signaling mediates homeostatic synaptic plasticity at the inhibitory synapses of mouse visual cortex

Authors: *L. R. ZHONG¹, X. C. CHEN², T. C. SUDHOF³, L. CHEN⁴

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Abstract: Homeostatic synaptic plasticity is a synaptic mechanism through which the nervous system adjusts synaptic excitation and inhibition to maintain network stability. Retinoic acid (RA) and its receptor RAR α have been established as critical mediators of homeostatic synaptic plasticity. *In vitro* studies reveal that RA signaling enhances excitatory synaptic strength and decreases inhibitory synaptic transmission. However, it is unclear whether RA-mediated homeostatic synaptic plasticity occurs *in vivo*, and if so, whether it operates at specific types of synapses. Here, we examine the impact of RA signaling in the monocular zone of the mouse primary visual cortex (V1m). Exogenous RA treatment in acute cortical slices resulted in a reduction in miniature inhibitory post-synaptic currents (mIPSCs) of layer 2/3 pyramidal neurons (PNs), an effect mimicked by visual deprivation induced by binocular enucleation in post-critical period animals. Postnatal deletion of RAR α blocked RA's effect on mIPSCs. Cell type-specific deletion of RAR α revealed that RA acted specifically on parvalbumin (PV)-expressing interneurons. RAR α deletion in PV+ interneurons also blocked visual deprivation-induced changes in mIPSCs, demonstrating the critical involvement of RA signaling in PV+ interneurons *in vivo*. Moreover, visual deprivation-induced downregulation of synaptic inhibition was absent in the visual cortical circuit of constitutive and PV-specific *Fmr1* KO mice, strongly suggesting a functional interaction between FMRP and RA signaling pathways. Taken together, our results demonstrate that RA signaling acts as a key component for homeostatic regulation of synaptic transmission at the inhibitory synapses of the visual cortex.

Disclosures: L.R. Zhong: None. X.C. Chen: None. T.C. Sudhof: None. L. Chen: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH086403
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NIH Grant HD084215

Title: Whisker-dependent sensory processing requires cortical retinoic acid signaling

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Abstract: Retinoic acid (RA) and its receptor (RAR α) are critical molecules in synaptic homeostatic plasticity through regulation of activity-dependent translation at excitatory and inhibitory synapses. However, *in vivo* studies elucidating the functional relevance of synaptic RA signaling have not been established. Here, we applied multiple genetic manipulations to delete RAR α postnatally in specific populations of cortical neurons, and asked whether synaptic RA signaling is involved in cortical information processing *in vivo* using behavioral assays and transcranial two-photon imaging. Conditional ablation of RAR α in mice via a CaMKII α -Cre or a layer 5-Cre driver line or via somatosensory cortex-specific viral expression of Cre-recombinase impaired whisker-dependent texture preference and discrimination, suggesting a critical requirement of RAR α expression in L5 pyramidal neurons of somatosensory cortex for normal tactile sensory processing. Transcranial two-photon imaging revealed a significant increase in dendritic spine elimination on apical dendrites of somatosensory cortical layer 5 pyramidal neurons in these mice, which was rescued by whisker trimming, indicating that the enhancement of spine elimination is whisker experience-dependent. In addition, in RAR α -deficient mice both texture discrimination and excessive spine pruning was improved by exposure to an enriched environment. Thus, we provide evidence that RA signaling through RAR α is essential for experience-dependent cortical circuit remodeling and sensory processing in the somatosensory cortex.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01EY025613

Title: Brain state modulation of synaptic plasticity: Addressing roles of sleep in homeostasis and the segregation of plasticity

Authors: *B. A. CARY¹, G. TURRIGIANO²

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Abstract: Sleep's function in modulating synaptic strength and plasticity remains deeply mysterious. Researchers have variously proposed that sleep stabilizes, strengthens, weakens, or even prunes synapses. Previous studies have often been limited by not properly controlling for circadian period, only indirectly measuring synapse strengths, or not considering differences between neuronal subtypes. In order to directly measure synaptic strength as a function of time spent asleep or awake, and to explicitly compare different brain regions, we developed a real-time sleep/wake classification system that allowed us to accurately classify a rat's ongoing sleep state history. Using this approach, we captured periods when an animal had experienced a recent sleep- or wake-dense period within a defined circadian window, and then harvested brain slices for acute *ex vivo* electrophysiology. In order to probe for global changes in postsynaptic strength that might be driven by prolonged periods of sleep or wake, we measured miniature excitatory postsynaptic currents (mEPSCs) from L2/3 or L4 pyramidal neurons in both Frontal Cortex (FC) and Visual Cortex (VC). There was no difference in mEPSC amplitude in either brain region in slices harvested after sleep or wake dense periods (VC: n=42,32, p>0.8 FC: n=30,28, p>0.9). However, there was a small but significant shift in the mini frequency distribution towards higher frequency after wake-dense episodes in the FC only ($p < 1e^{-5}$), which suggests sleep/wake have distinct net effects on synapses in different regions of cortex. Work is underway to record from spontaneous wake dense episodes during the opposite circadian time, allowing us to directly ask if circadian rhythm might be responsible for net changes in synaptic strengths. Lastly, although sleep and wake may have minimal functional impact on synapses under basal conditions, the induction of synaptic plasticity may still be segregated to different brain states in the context of learning or experience-dependent plasticity. To explore this, we are piloting experiments to selectively induce long-term potentiation or homeostatic plasticity at thalamocortical synapses *in vivo* during sleep or wake to directly test if brain state gates the induction of Hebbian or homeostatic forms of plasticity.

Disclosures: B.A. Cary: None. G. Turrigiano: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.06/E23

Topic: B.07. Synaptic Plasticity

Support: Keck Foundation

Title: Circuit-specific DNA modifications change as photoperiod-induced neurotransmitter plasticity declines with aging

Authors: ***R. PRITCHARD**¹, H. CHEN¹, N. SPITZER², D. DULCIS¹

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Abstract: Chronic exposure to short-day (5L:19D) or long-day (19L:5D) photoperiods alters the number of dopamine (DA)- and somatostatin (SST)- expressing neurons in the para- and periventricular nuclei (PVN) of the adult rat hypothalamus via neurotransmitter switching. Our previous studies identified reserve pool neurons that switch identity via photoperiod-dependent transcriptional regulation and the resulting changes in behavior (Dulcis et al., 2013). We have now extended these findings by examining this plasticity throughout stages of aging. We then investigated changes in epigenetic patterns of histone acetylation and DNA methylation through which changes in environmental light and stress may regulate transmitter respecification. Rats at 1, 3, 12, and 18 months of age were exposed for 1 week to either a long day, normal day (12L:12D) or short day. Brains were processed for immunohistochemical analysis of epigenetic markers for *de novo* DNA methylation (DNMT3a) and histone H3 acetylation (H3) in DA- and SST-expressing PVN neurons. Our data indicate that DA/SST plasticity in the PVN occurs early in life and is maintained throughout adulthood. However, DA plasticity is reduced at 12 months and abolished in both SST+ and TH+ (DA) cell types by 18 months. Methylation increased following short-day photoperiod in both cell types in younger animals while an overall increase in methylated SST+ neurons paralleled neuroplasticity reduction at 12 and 18 months. Histone acetylation at 3 months was increased in DA neurons and decreased in SST neurons following 5L:19D photoperiod. While H3 acetylation and methylation patterns changed at the circuit-level, the total number of acetylated and methylated PVN neurons remained constant, revealing the importance of studying epigenetic mechanisms in identified cell types rather than by whole tissue analysis. The linkage between age-dependent reduction in neurotransmitter plasticity and associated changes in DNA methylation and acetylation patterns, within cells that switch transmitter identity, provides new insights regarding the stages of neuroplasticity in the aging brain. The results are expected to be useful for developing approaches for efficacious, non-invasive treatment in disorders characterized by neurotransmitter dysfunction.

Disclosures: **R. Pritchard:** None. **H. Chen:** None. **N. Spitzer:** None. **D. Dulcis:** None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 038.07/E24

Topic: B.07. Synaptic Plasticity

Support: UCSD Health Sciences Research Grant # RS155R awarded to Davide Dulcis
NIMH R01 MH106865 awarded to Andre Der-Avakian

Title: Social stress induces neurotransmitter switching in the dorsal raphe nucleus

Authors: *N. PRAKASH, C. STARK, A. DER-AVAKIAN, D. DULCIS
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Abstract: Anhedonia, or lack of pleasure, is a core symptom of major depressive disorder and is common in other mood disorders. Chronic stress is known to induce anhedonia in human subjects and this phenomenon is recapitulated in rodent behavioral models¹. Since stress has been shown to elevate both neuronal activity and the level of serotonin² in the dorsal raphe nucleus (DR), we hypothesized that the newly discovered neurotransmitter switching³ occurs in response to stress-induced neuronal activity and contributes to susceptibility to stress. We used intracranial self-stimulation (ICSS) of the posterior lateral hypothalamus (part of the brain's reward circuitry) to measure anhedonia in male Wistar rats. After 21 days of social defeat stress and daily measurements of ICSS reward thresholds, rat brains were processed by immunohistochemistry with markers for neuronal activity and neurotransmitter expression. Number of cells expressing one or more markers of neurotransmitters activity was quantified. Social defeat elevated reward thresholds, indicating anhedonia. As compared to controls, stressed animals displayed a ~30% increase in number of serotonergic neurons, marked by tryptophan hydroxylase (TPH2), in the ventral DRv. This was accompanied by an increase in nitergic expression, marked by neuronal nitric oxide synthase (nNOS) within the serotonergic population. The total number of neurons was unchanged, indicating that preexisting differentiated neurons acquired TPH2 and nNOS expression during chronic stress. Other DR sub-nuclei did not show any changes in TPH2 expression. Ongoing experiments will reveal the identity and activity-dependent recruitment of the reserve pool of neurons acquiring the TPH2 phenotype following chronic stress. Our results also indicated that non-serotonergic neurons in the DRv were less active in stressed animals as measured by cFos expression six hours after the last social defeat encounter. Collectively, these results suggest that social stress may produce reward impairments via modulation of neuronal activity and recruitment of new serotonergic cells in the DRv.

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Disclosures: N. Prakash: None. C. Stark: None. A. Der-Avakian: None. D. Dulcis: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

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Program #/Poster #: 038.08/E25

Topic: B.07. Synaptic Plasticity

Support: NIH Grant

Title: Nicotine-induced neurotransmitter plasticity in the substantia nigra

Authors: *I.-C. LAI, B. ROMOLI, S. POWELL, D. DULCIS
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Abstract: Cigarette smoking is generally known for its detrimental effects on health; however, extensive epidemiological studies have indicated inverse correlation between smoking and Parkinson's Disease (PD), a progressive neurodegenerative disorder characterized by loss of dopaminergic (DA) neurons in the substantia nigra (SN). Subsequent studies have shown that nicotine protects DA neurons against nigrostriatal damage in PD primate and rodent models. Nicotine became the focus of these studies due to its well-known ability to modulate function and activity of midbrain DA neurons. Because altered circuit activation can induce neurons to acquire a DA phenotype in the mature brain (Dulcis et al. 2013 Science), we hypothesized that chronic nicotine treatment in adult mice contributes to neuroprotection against nigrostriatal damage in an animal model of PD via a mechanism of neurotransmitter (NT) plasticity. Nicotine was given to adult (P60) mice in drinking water for two weeks. Brains of various transgenic reporter mouse lines were subsequently processed for immunohistochemistry and retrobead tracing for detection of NT-expressing cell types, such as tyrosine hydroxylase (TH) and vesicular GABA transporter (VGAT), in the SN and their connectivity. Selective overexpression of human alpha-synuclein in midbrain DA neurons was used as a PD mouse model (Lin et al., 2012 JN).

Our findings showed that chronic nicotine treatment significantly increased DA (TH+) expression within a pool of SNr (pars reticulata) GABAergic neurons that express transcription factors associated with DA differentiation, such as *Nurr1* and *Foxa2*, prior to nicotine exposure. Importantly, our retrograde labelling experiments showed that this GABAergic neuronal pool in the SNr projects to the caudate nucleus, the same target of SNc (pars compacta) DA neurons.

Ongoing behavioral experiments on a PD mouse model will reveal whether nicotine-induced neurotransmitter plasticity ameliorates any motor deficits in these mice.

Our findings indicate that neurotransmitter plasticity occurs in the SN in response to chronic nicotine treatment. Understanding its role in neuroprotection against nigrostriatal damages in PD could reveal insights that might lead to the development of new treatments for Parkinson's Disease.

Disclosures: **I. Lai:** None. **B. Romoli:** None. **S. Powell:** None. **D. Dulcis:** None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 038.09/E26

Topic: B.07. Synaptic Plasticity

Support: NIH Grant

Title: Neonatal nicotine exposure primes non-dopaminergic VTA neurons to express dopamine in response to adult nicotine consumption

Authors: ***B. ROMOLI**¹, A. F. LOZADA³, I. M. SANDOVAL⁴, F. P. MANFREDSSON⁴, D. K. BERG⁵, D. DULCIS²

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Abstract: Nicotine is a psychoactive substance that induces addiction through neuroplasticity affecting the function of the Ventral Tegmental Area (VTA) and dopamine (DA) release in the reward circuitry. Although DA and other neurotransmitters (NT) expressed by differentiated neurons were generally believed to be fixed throughout the life of a neuron, we have previously shown that altered neuronal activity can change NT expression both in the developing (Dulcis et al., 2008, 2017) and adult (Dulcis et al., 2013) brain. Here, we investigated the effect of neonatal nicotine (NN) exposure on NT plasticity of VTA DA neurons. Nicotine-loaded osmotic pumps were implanted in lactating mice to deliver 2 mg nicotine/Kg/day to the pups from postnatal day 2 (P2) to P16. Our findings indicate that NN exposure potentiates nicotine preference in adult (P90) mice when tested with the two-bottle choice test and significantly increases nicotine-mediated calcium responses of VTA neurons. Brains were harvested after NN exposure (P16) as well as in the adult before (P90) and after (P120) the second nicotine challenge, then processed for tyrosine hydroxylase (TH) and nuclear receptor related-1 protein (Nurr1) immunohistochemistry. We discovered that NN exposure induces ectopic Nurr1 expression

within VTA glutamatergic neurons and that adult nicotine exposure significantly increases both the total number of DA neurons and the co-expression with glutamate in the VTA of NN-exposed mice. To investigate the activity dependence and the role of Nurr1 on induction of nicotine preference and DA plasticity, we virally overexpressed Nurr1 and chemo-genetically (DREADDs) altered neuronal activity in selected classes of non-DAergic VTA neurons using VGLUT2-cre and VGAT-cre mouse line, respectively. Our results showed that Nurr1 induces an increase in nicotine preference when paired to activity manipulation. An ongoing miRNA approach used to downregulate Nurr1 expression in glutamatergic neurons will reveal whether Nurr1 expression is necessary for non-DAergic neurons to acquire a DAergic identity. To determine the effects of NN-induced DAergic switching in the VTA on motivation and reward-seeking behaviors we performed behavioral tests, such as progressive ratio, conditioned place preference, and ethanol consumption. Given the high prevalence of smoking and nicotine replacement treatments during pregnancy and breastfeeding, DA plasticity in the VTA may provide a new critical link between developmental exposure to drugs of abuse and adult susceptibility to addiction.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

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Program #/Poster #: 038.10/E27

Topic: B.07. Synaptic Plasticity

Support: DFG, CRC 1080, C02
UM Mainz, IFF1

Title: Adaptive mechanisms of inter-hemispheric connectivity and GABAergic function in the early phase after unilateral traumatic brain injury in mice

Authors: ***T. MITTMANN**, Q. WANG, M. BILLAUD, T. NOVKOVIC
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Abstract: Unilateral traumatic brain injury (TBI) is known to induce functional changes of neuronal circuits in the vicinity of the mechanically induced lesion. TBI can also lead to epileptogenesis month to years later as observed in rodents and humans. Recently, we disclosed an expression of neuronal hyperactivity in neurons of the primarily undamaged, contralateral hemisphere already 24 hours after the injury. The underlying cellular mechanisms are not understood. The aim of the present study was to examine the role of synaptic inputs from corpus callosum on the hyperactivity in the primarily undamaged contralateral hemisphere. Unilateral

TBI was induced in vivo under anesthesia by use of a controlled mechanical impactor. Twenty-four hours later whole-cell patch-clamp recordings were performed from pyramidal neurons in layer V in acute brain slices of contralateral hemisphere. Stimulation of callosal fibers led to a change of paired-pulse ratio of evoked EPSCs (eEPSCs), an increased success rate of eEPSCs following minimal synaptic conditions and to an elevated frequency, but not amplitude of miniature EPSCs in layer V neurons. We applied a binomial model of synaptic transmission, originally used by Katz (1969). In this model the mean postsynaptic response is a product of quantal size, number of available vesicles and probability of release. By analyzing spontaneous EPSCs following high-frequency stimulation in the context of this model we observed (in line with our other data) a facilitated presynaptic function of glutamatergic callosal synapses. Furthermore, we investigated functional changes of specific subtypes of GABAergic interneurons in the contralateral hemisphere of GAD67-GFP mice at 24 hours after TBI. Whole-cell patch clamp recordings were performed from visually identified GFP-labeled GABAergic neurons in acute cortical slices. The subtype of each recorded GABAergic neuron was defined by its properties of action potential firing during intrinsic depolarization. Here the population of non-fast spiking interneurons (VIP- and SST-positive interneurons) revealed an increased glutamatergic strength as shown by the increased frequency, but not amplitude, of sEPSCs in these interneurons. All together our data suggest that the previously observed hyperactivity of neuronal circuits in the contralateral hemisphere post TBI is caused, at least in part, by increased glutamatergic inputs originating from the ipsilateral hemisphere. Our previous observation of a general, adaptive impairment of GABAergic inhibition does not account for the population of non-fast spiking interneurons, since they receive a larger excitatory input.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.11/E28

Topic: B.07. Synaptic Plasticity

Support: R01EY012124

R01EY016431

R01EY025922

T32EY007143

T32HL110952

Title: Two distinct mechanisms for experience-dependent homeostasis

Authors: *M. BRIDI¹, R. DE PASQUALE⁶, C. L. LANTZ⁷, Y. GU⁹, A. BORRELL⁸, S.-Y. CHOI¹⁰, K.-W. HE¹¹, T. T. TRAN², S. Z. HONG³, A. DYKMAN⁴, H.-K. LEE⁵, E. M.

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Abstract: Models of firing rate homeostasis predict that decreasing neuronal activity by sensory deprivation will enhance synaptic function. Accordingly, pharmacological or molecular manipulations that further reduce activity during sensory deprivation are predicted to further enhance synaptic function. We tested this prediction in two models of homeostasis: synaptic scaling and the sliding modification threshold for synaptic plasticity. We eliminated visually evoked activity in mice using 2d dark exposure (DE), while reducing the remaining spontaneous activity by enhancing inhibition (with the GABA_A agonist diazepam or the peptide NRG1 delivered i.p.). We then performed whole-cell patch clamp recordings in V1 slices. We assessed the threshold for LTP and LTD using pairing protocols, and synaptic scaling by measuring mEPSCs. Contrary to expectations, reducing activity during DE prevented, rather than enhanced, both the sliding of the plasticity threshold and the increase in mEPSC amplitude. Reducing spontaneous activity during DE also prevented the DE-mediated increase in GluN2B (measured as the evoked NMDA-receptor current decay and sensitivity to ifenprodil), indicating that spontaneous activity during DE is required to shift the threshold for LTP induction. Blocking activation of GluN2B-containing receptors during DE prevented the increase in mEPSC amplitude, suggesting that the lowered LTP induction threshold, rather than non-Hebbian synaptic scaling, is responsible for increased mEPSC amplitude during DE. However, when neuronal activity was reduced to a greater extent (using THIP, an agonist of tonic inhibition, i.p.), mEPSC amplitude increased in an NMDAR-independent manner. These results fit a model in which two distinct mechanisms operate within different ranges of neuronal activity to homeostatically regulate synaptic strength. During DE, the plasticity threshold slides to favor LTP, and spontaneous activity can then induce LTP to increase mEPSC amplitude. When neuronal activity is reduced more severely, synaptic scaling mechanisms are engaged to increase mEPSC amplitude.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.12/E29

Topic: B.07. Synaptic Plasticity

Support: NIH R01-EY014882

Title: Role of neuronal activity and metaplastic state in homeostatic synaptic plasticity

Authors: ***B. D. GRIER**^{1,2}, V. CHOKSHI^{3,2}, A. DYKMAN⁴, C. L. LANTZ⁵, E. NIEBUR^{1,2}, E. M. QUINLAN⁵, H.-K. LEE^{1,2}

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Abstract: Synapses show a remarkable ability to undergo adaptive changes in response to varying information processing needs of a system. Homeostatic plasticity represents one such form of functional adaptation and is characterized by scaling of synaptic strength in response to changes in neuronal activity. Prolonged changes in visual experience drive homeostatic plasticity at excitatory synapses, which has been extensively studied *ex vivo* in primary visual cortex (V1) layer 2/3 (L2/3) pyramidal neurons (Goel et al., 2006; Goel & Lee, 2007). The precise nature of the pre- and post-synaptic neuronal activity required to drive such plasticity *in vivo* remains unknown, however. Here we developed an *ex vivo* stimulation paradigm to study what aspects of *in vivo* activity patterns result in homeostatic synaptic plasticity. This paradigm not only allows parametric analysis of changes resulting from different *in vivo* activity patterns, but also does so in the context of mostly intact *in vivo* circuitry. The critical need to study homeostatic synaptic plasticity in the context of *in vivo* circuitry is highlighted by the finding that homeostatic synaptic changes can be restricted to a certain set of inputs onto cortical neurons (Petrus et al., 2015). By stimulating V1 layer 4 cells in acute cortical slices to fire with the activity pattern of V1 layer 4 cells *in vivo*, we have observed homeostatic synaptic plasticity in L2/3 pyramidal neurons. Further, by employing computational algorithms we have begun to determine the features of neuronal firing patterns that are key to driving homeostatic synaptic scaling. Finally, our data suggest that homeostatic plasticity is not simply a function of changes in input activity. Rather, the metaplastic state of post-synaptic cells gives context to synaptic activity, thus yielding different homeostatic synaptic adaptation in response to the same pattern of activity.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.13/E30

Topic: B.07. Synaptic Plasticity

Support: NIH/NINDS 16-PAF01522
NIH 14-PAF02579

Title: Homeostatic regulation of intrinsic excitability in fragile x syndrome

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Abstract: Fragile X Syndrome (FXS), caused by transcriptional silencing of the *fmr1* gene, is the most common inherited form of intellectual disability and the leading monogenic cause of Autism Spectrum Disorder. In addition to cognitive and social deficits, FXS patients experience hyperactive behavior, seizures, and anxiety suggesting that neural circuit instability is an important feature of FXS. The *fmr1* product FMRP is an RNA binding protein that controls the translation of genes that encode various synaptic proteins and regulate neuronal plasticity and activity. Here, we investigate the role of FMRP in homeostatic regulation of intrinsic neuronal excitability in cultured hippocampal neurons. Mechanisms that facilitate homeostatic plasticity aim to stabilize activity in neuronal circuits through compensatory changes in synaptic function and/or intrinsic excitability. Compensatory changes in intrinsic excitability typically emerge slowly following chronic network silencing with tetrodotoxin. By contrast, we find that direct block of AMPA-mediated synaptic activity drives rapid homeostatic increases in intrinsic excitability that feature two distinct components: 1) a reduction in action potential (AP) threshold, and 2) a decrease in spike-frequency adaptation during prolonged current steps. Using RNAi-mediated FMRP knockdown, FMRP KO mice, and FMRP KO rats, we find that FMRP is critical for shifting AP threshold during AMPAR blockade but is not required for changes in spike-frequency adaptation. In part, FMRP regulates AP threshold by controlling synthesis and expression of the voltage-gated Na⁺ channel NaV1.2 in the axon initial segment. These results define a novel homeostatic mechanism whereby FMRP contributes to controlling neural activity.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Topic: B.07. Synaptic Plasticity

Support: NIH/NINDS 16-PAF01522
NIH 14-PAF02579

Title: Differential roles for unique l-type Ca^{2+} -channel subtypes in homeostatic synaptic scaling

Authors: *A. CHEN¹, S. RICE², G. G. MURPHY³, M. A. SUTTON³

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Abstract: Voltage-gated Ca^{2+} -channels (VGCCs) provide a pivotal link between membrane depolarization, calcium influx, and activity-dependent changes in gene expression. L-type Ca^{2+} -channels (LTCCs) are perhaps the best characterized of the VGCCs and these have been implicated in a number of important synaptic mechanisms. Often, the role of LTCCs in synaptic plasticity has been inferred by using a variety of dihydropyridine antagonists such as nifedipine, nimodipine, or verapamil. Blocking LTCCs with these agents has been shown to induce a rapid form of homeostatic synaptic plasticity (HSP) at synapses, but the role of LTCCs in classic homeostatic scaling has been difficult to define. Here, we provide novel evidence demonstrating non-redundant roles for unique LTCC subtypes in HSP expressed by hippocampal neuron cultures isolated from $Ca_v1.2$ and $Ca_v1.3$ mutant mice. We find that neurons lacking different LTCCs show deficient scaling of miniature excitatory post-synaptic currents (mEPSCs) during chronic activity silencing with tetrodotoxin (TTX). Recruitment of new α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) to synapses, as assessed by immunolabeling and imaging, during activity silencing is also compromised in LTCC subtype knockouts. Together, our results demonstrate an important role for L-type Ca^{2+} -channels in homeostatic synaptic scaling and open up new opportunities to understand the activity-dependent sensor that couples chronic alterations in activity with appropriate changes in gene expression.

Disclosures: A. Chen: None. S. Rice: None. G.G. Murphy: None. M.A. Sutton: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.15/E32

Topic: B.07. Synaptic Plasticity

Support: NIH/NINDS 16-PAF01522

NIH 14-PAF02579

Title: Activity-dependent proteasome trafficking in axons underlies state-dependent expression of synaptic homeostasis

Authors: *J. C. ALTHAUS¹, F. E. HENRY⁵, S. J. JAKAWICH², H. NASSER⁶, V. A. CAZARES¹, C. CARRUTHERS², E. L. STUENKEL³, G. N. PATRICK⁷, M. A. SUTTON⁴

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Abstract: Precisely tuned regulation of pre and post-synaptic communication depends on the ability to adjust synaptic protein levels via coordinated protein synthesis and degradation mechanisms. Previous work has demonstrated activity-dependent proteasome recruitment into dendritic spines in response to synaptic stimulation, indicating that remodeling the synaptic landscape via active degradation is likely an important aspect of postsynaptic functional plasticity. In axons, where the abundance of proteasomes is dramatically lower than in dendrites, the redistribution of the proteasome to appropriate synaptic terminals could be a critical mechanism governing protein degradation in the presynaptic compartment. Indeed, we report here that intrinsic firing governs activity-dependent proteasome trafficking to and from synaptic terminals in axons of cultured hippocampal neurons, and this dynamic proteasome localization is critical for trans-synaptic signaling to homeostatically adjust presynaptic neurotransmitter release. Using epitope- and fluorescently-tagged subunits of the 19S proteasome, we find that increasing neuronal firing rates enriches proteasome accumulation at synaptic terminals, whereas inhibiting neuronal firing results in a dramatic redistribution away from synaptic terminals to non-synaptic areas. This altered localization is due, at least in part, to an activity-dependent active sequestration mechanism at presynaptic terminals, as revealed by live monitoring of fluorescence persistence after synaptic photoactivation of GFP-tagged proteasomal subunits. Moreover, we find that activity dependent phosphorylation of the Rpt6 subunit of the 19S proteasome is necessary and sufficient for axonal proteasome redistribution, and that this altered localization plays a critical role in establishing retrograde homeostatic changes in presynaptic function after loss of postsynaptic drive. Together, our data reveal that dynamic redistribution of the proteasome is a novel mechanism whereby the activity-dependent “state” of synaptic compartments determines the specific forms of plasticity they can exhibit.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.16/E33

Topic: B.07. Synaptic Plasticity

Support: NIH Grant HD084215

Title: Enriched environment rescues behavioral abnormalities in a mouse model of fragile X syndrome

Authors: *J. LI, K. L. ARENDT, Y.-T. HSU, R. JIANG, L. CHEN
Neurosurg., Stanford Univ., Stanford, CA

Abstract: Fragile-X Syndrome (FXS), caused by the loss of function of the *FMR1* gene, is the most common form of inherited intellectual disability and a monogenic cause of autism spectrum disorder. Previous studies in our lab identified a key role of retinoic acid (RA) in homeostatic synaptic plasticity. RA mediated homeostatic synaptic plasticity is completely absent at both excitatory and inhibitory synapses in the hippocampus of *Fmr1* knockout mice as well as in human neurons differentiated from FXS patient induced pluripotent stem cells and *FMR1* conditional knockout human embryonic stem cells, indicating that RA-dependent homeostatic synaptic plasticity may contribute to FXS pathophysiology.

Homeostatic synaptic plasticity is a form of non-Hebbian plasticity that enables neural network to maintain stability over long periods of altered synaptic activity. In the absence of RA-mediated homeostatic synaptic plasticity, hippocampal Hebbian plasticity and animal learning are severely altered in animals with enriched environment (EE) experience. To investigate whether impaired RA signaling drives behavioral changes in FXS, we systematically performed a series of behavioral tests in *Fmr1* knockout mice. In animals with normal home cage (HC) experience, we observed impairment in hippocampus-dependent learning tasks including water T maze test, passive avoidance test and contextual fear conditioning test. Interestingly, EE exposure, which engages a large population of neurons in the hippocampus, alleviate the hippocampus dependent learning and memory deficits in *Fmr1* knockout mice. In addition, *Fmr1* knockout mice performed similarly to wild type mice in the Y maze and hot plate tests, indicating intact working memory and nociception. To understand the physiological effect of EE and potential roles of RA signaling in FXS mice, we recorded EPSCs from hippocampal CA1 region. RA application increased EPSC in HC-reared wildtype mice, while the increase was absent in *Fmr1* knockout mice, indicating the impairment of RA signaling in FXS mice. Interestingly, both wildtype and *Fmr1* knockout mice showed no response to RA treatment after EE exposure, likely because EE engages RA signaling and occludes further response to RA stimulation. Taken together, these data suggest that EE stimulation has beneficial effect on the pathological FXS phenotype, which may be achieved through regulating RA mediated homeostatic synaptic plasticity.

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Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

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Program #/Poster #: 038.17/E34

Topic: B.07. Synaptic Plasticity

Support: NIH R01EY025613

Title: Sleep temporally segregates the expression of downward firing rate homeostasis *in vivo*

Authors: *A. TORRADO PACHECO¹, K. B. HENGEN², G. G. TURRIGIANO¹

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Abstract: The role of sleep in regulating plasticity in the brain remains controversial despite decades of research into the topic. It has been hypothesized that sleep's function is to allow for homeostatic plasticity mechanisms to re-normalize activity following learning-induced changes. Previously we investigated this question by perturbing firing in primary visual cortex (V1) of rats via monocular deprivation (MD) to induce homeostatic compensation, while monitoring animals' sleep-wake state. MD caused an initial depression in firing after 2 days, followed by a homeostatic return to baseline levels after an additional 3-4 days. This upward firing rate homeostasis (FRH) occurred exclusively during waking, challenging the idea that homeostatic plasticity is restricted to periods of sleep. This work left open two important questions: a) whether the homeostatic regulation of cortical firing is a bi-directional process; b) whether the state dependence seen for upward FRH holds true for plasticity in the opposite direction. To answer these we recorded single-unit activity in V1 of freely behaving rats using chronic *in vivo* electrophysiology. We follow individual neurons' activity continuously over 12 days to show that eye re-opening (ER) after 5 days of MD causes a 2-fold increase in firing rate that peaks after 24 hours. This is followed by a slower recovery of activity, with each neuron's firing returning close to its original baseline value. This demonstrates for the first time that neuronal firing rates *in vivo* are subject to bi-directional homeostatic regulation. Additionally we classified the behavioral state of animals, and analyzed when downward FRH occurred. Wake- or sleep-dense epochs (defined as 3-hour windows with at least 70% wake or sleep) during the period of FRH did not affect the activity of control neurons, but the decrease in firing occurred exclusively during sleep-dense epochs (30% decrease). We also found a negative correlation ($r = -0.15$, $p = 0.02$) between time spent asleep and fractional change in firing rate. Our data show that homeostatic plasticity *in vivo* is regulated differently depending on the direction of change, with upward FRH promoted by wake, and downward FRH promoted by sleep. This reveals that vigilance state temporally segregates brain plasticity, and that this regulation is much more complex than previously thought.

Disclosures: A. Torrado Pacheco: None. K.B. Hengen: None. G.G. Turrigiano: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 038.18/E35

Topic: B.07. Synaptic Plasticity

Support: BIU2

Title: Viral tools in the analysis of neuronal circuits

Authors: *C. R. BATTAGLIA¹, B. HENGERER², T. M. BOECKERS¹

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Abstract: In the past few years, designer receptors exclusively activated by designer drugs, known as DREADDs, have emerged as powerful new tools for the study of neuronal circuits. DREADDs are designer G protein-coupled receptors (GPCRs) sensitive to the inert compound clozapine-N-oxide (CNO). In order to determine whether neurons drive a particular behavior, a DREADD can be expressed by intracerebral microinjection into selected cell populations. With two different DREADDs, responding to different exogenous ligands, it is possible to control the neuronal activity in a bidirectional way: exciting a particular neuronal population and then rapidly inhibiting it to provide conclusive evidence of their involvement in a specific behavior. We tested in cultures hippocampal neurons (*in vitro*) the AAV2-hSyn-DIO-hM3D(Gq)mCherry and the AAV9-Cre-GFP for functionality before applying these constructs in the *in vivo* situation. To that end we employed the Synaptotagmin assay, considering that Synaptotagmin1 triggers the calcium-induced release of neurotransmitters from the synaptic vesicles. We show that the hM3D(Gq)-virus readily activates the neuronal activity (neuronal firing), after the CNO administration.

Having these findings in mind, the aim of our study is to investigate phenotypic differences core areas-related in mouse model by DREADD technology.

Disclosures: C.R. Battaglia: None. B. Hengerer: None. T.M. Boeckers: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 038.19/E36

Topic: B.07. Synaptic Plasticity

Support: BIU2

Title: Characterization of synapses in human iPSCs-derived organoids

Authors: *M. MALARA¹, S. PFAENDER¹, M. SCHOEN¹, B. HENGERER², T. M. BOECKERS¹

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Abstract: Cerebral organoids from human induced pluripotent stem cells (hiPSC) represent a three-dimensional organoid culture system, that reproduces brain-like regions *in vitro*. The approach is based on the intrinsic self-organizational capacity of the cells to pattern, specify, and generate cerebral tissue. These organoids develop from embryoid bodies (EBs) grown initially in embryonic stem cell medium with low bFGF and ROCK inhibitor. At later steps of the protocol the establishment of neural identity and a 3D structural organization is reached.

Our study focuses on hiPSC and the establishment of a human iPSC-derived cerebral organoid model for the analysis of neurodevelopmental disorders. We could successfully establish the cerebral organoid model and confirmed the identity of different brain subregions. We identified cortex-like regions, characterized by genetic programs very similar to human fetal tissue that should enable us to analyze human cortical development in the organoid culture system.

Furthermore, we analyzed different stages of organoid development and confirmed the maturity of neurons, glial cells and the presence of morphologically mature synapses by performing immunohistochemistry with antibodies directed against pre- and postsynaptic marker proteins.

Then, we could use cryo-electron microscopy in order to analyze the ultrastructure of cerebral organoids and to confirm the presence of mature synapses. Finally, we could successfully apply the CLARITY approach, through which we could obtain a better overview of the “mini-brain” after different staining approaches. The cerebral human organoid model system might reflect early developmental mechanisms of brain development allowing to study neurodevelopmental diseases in more detail. Especially the analysis of early wiring between organoid subregions and synaptogenesis might help to understand subtle alterations that might occur during early steps of human brain development.

Disclosures: M. Malara: None. S. Pfaender: None. M. Schoen: None. B. Hengerer: None. T.M. Boeckers: None.

Poster

038. Synaptic Plasticity: Homeostatic Plasticity II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 038.20/E37

Topic: H.01. Animal Cognition and Behavior

Support: James McDonnell Foundation

Title: Representation of latent states in a non-spatial cognitive map

Authors: *X. WANG, C. CHEN, I. BARREIROS, N. NYBERG, V. SAMBORSKA, M. E. WALTON, T. BEHRENS

Oxford Univ., Oxford, United Kingdom

Abstract: Understanding the relationships between states in a task allows for quick and flexible inference on the basis of sparse observation. Such relational reasoning requires the representation of latent states which, although being unobservable, play a key role in enabling subjects to quickly predict changes of observable states before experiencing them. However, little is known about how the neural codes of latent states are built and represented in the brain. In the current study, we trained rats to learn a cognitive map of auditory cues which are anti-correlated in reward probabilities. After nose-poking to initiate a cue in each trial, the rat can either choose to accept the current cue by pressing the lever to check whether this cue is rewarded, or choose to reject this cue by nose-poking again the port. We found that the rats could learn about the anti-correlated relationship between two cues and guide their choice using this knowledge of latent state. Then we recorded the spiking activities of multiple neurons by wireless silicon probes in mPFC and IOFC . Our preliminary neural data showed that the neural response could reflect the rat's current belief about the relationship between cues.

Disclosures: X. Wang: None. C. Chen: None. I. Barreiros: None. N. Nyberg: None. V. Samborska: None. M.E. Walton: None. T. Behrens: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.01/E38

Topic: B.10. Epilepsy

Support: R01NS093045

Title: Noninflammatory homeostatic changes of microglia promote the development of spontaneous recurrent seizures

Authors: X. ZHAO, *Y. HUANG

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Abstract: Microglia are well known to play a critical role in maintaining brain homeostasis. However, evidence remains lacking for any role of perturbed microglial homeostatic activity in epileptogenesis. Here, we demonstrate that elevated mTOR signaling in mouse microglia causes the cells to adopt a non-inflammatory reactive phenotype, including an amoeboid-like morphology, increased proliferation, robust phagocytosis activity, and strong expression of the microglial activation marker CD68, but without the induction of pro-inflammatory cytokines. We further provide evidence that these non-inflammatory changes in microglia disrupt homeostasis of the CNS, leading to reduced synapse density, marked microglial infiltration into hippocampal pyramidal layers, moderate neuronal degeneration, and massive proliferation of astrocytes. Moreover, the mice thus affected develop severe early-onset spontaneous recurrent

seizures. Therefore, we have revealed a novel epileptogenic mechanism that is independent of the microglial inflammatory response. Our data suggest that microglia could be an opportune target for epilepsy prevention.

Disclosures: X. Zhao: None. Y. Huang: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.02/E39

Topic: B.10. Epilepsy

Support: Dravet Syndrome Foundation
UC Davis MIND Institute

Title: Seizure susceptibility in a novel preclinical mouse model of Dravet syndrome

Authors: *A. ADHIKARI^{1,2}, N. A. COPPING^{1,2}, T. W. STRADLEIGH^{3,2}, I. ZDILAR^{3,2}, A. S. NORD^{3,2}, J. L. SILVERMAN^{1,2}

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Abstract: Dravet Syndrome (DS) is a rare neurological disorder caused by loss-of-function mutations of the Sodium channel gene (*Scn1a*) encoding voltage-gated sodium channel Nav1.1. It is characterized by frequent prolonged seizures, developmental delay, and cognitive and social impairments (Mahoney et al., 2009; Li et al., 2011; Miller et al., 2014). The majority of cases of DS are attributable to mutations of the gene; however, in 20% of DS cases, no mutation can be found in the protein coding regions of the *Scn1a* gene. Genetic engineering via the CRISPR/Cas9 system was used to generate C57BL/6N mutant mice with a deletion of h1b region, a principal regulatory region of *Scn1a* gene. We characterized this novel mouse model *Scn1a*^{h1b+/-} on a sequence of behavioral assays relevant to neurodevelopmental disorders (NDD), including DS, as well as control assays to ensure our complex behaviors are not confounded by physical health and/or motor ability. We used a developmental Fox battery that examined neonatal pups during post-natal day 2 to 12 every other day for body metrics, reflexes, strength, and coordination. In adults, we used a wide battery of assays relevant to NDD (Silverman et al., 2010). In *Scn1a*^{h1b+/-}, we also tested the threshold to seizures using latencies to myoclonic jerk, generalized tonic-clonic seizure, full tonic extension, and death using chemoconvulsants. We report a minimum of 50% mortality and spontaneous seizures in the *Scn1a*^{h1b-/-} and precisely quantified susceptibility to seizures in *Scn1a*^{h1b+/-} mice by significantly reduced latencies to myoclonic jerk, generalized clonic seizure, and tonic extension. We also define atypical spike patterns via

electroencephalogram (EEG) in *Scn1a*^{h1b+/-}. We generated and validated a novel model of DS and epilepsy confirmed phenotypes relevant to NDD and DS.

Disclosures: **A. Adhikari:** None. **N.A. Copping:** None. **T.W. Stradleigh:** None. **I. Zdilar:** None. **A.S. Nord:** None. **J.L. Silverman:** None.

Poster

039. Epilepsy

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Topic: B.10. Epilepsy

Support: NIH Grant R21NS095756
NIH Grant K01DA036751
NIH Grant T32MH014654
NIH Grant R01MH109260
NIH Grant R01NS49306
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Title: Investigation of long interspersed element-1 retrotransposon gene disruptions in the etiology of idiopathic temporal lobe epilepsy

Authors: ***G. A. DOYLE**¹, R. J. BUONO², T. N. FERRARO², R. CRIST³, B. C. REINER³, G. ARAUCO-SHAPIRO³, R. N. LEVINSON³, L. D. SHAH³, W. H. BERRETTINI³

¹Univ. Pennsylvania, Philadelphia, PA; ²Biomed. Sci., Cooper Med. Sch. of Rowan Univ., Camden, NJ; ³Ctr. for Neurobio. and Behavior, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Epilepsy affects 1% of the world population with one-third of patients being refractory to anti-epilepsy drugs. Most patients (60%) have no known symptomatic cause and are considered to have idiopathic or presumed genetic epilepsy. Temporal lobe epilepsy (TLE) is the most common form of focal or generalized epilepsy. Genome-wide association studies of patients with TLE have yielded little insight into the pathophysiology of this disorder, suggesting that rare heritable variants or *de novo* somatic mutations might be causative. We investigated whether somatic mutation involving long interspersed element-1 (LINE-1) retrotransposons might explain some idiopathic TLE cases. Patients with medication-resistant TLE underwent electroencephalograph-directed craniotomy in which the temporal lobe was resected. Samples of temporal cortex (BA38) from control subjects or TLE patients (N=33 each) were analyzed for LINE-1 content by PCR-based LINE-1 amplification and next-generation sequencing.

Bioinformatics analysis identified genomic positions of novel LINE-1 sequences. No statistically significant differences between cases and controls were observed for total known or novel LINE-1 sequences, or for *inter-genic*, *intra-genic* or *intra-exonic* LINE-1 sequences. However, LINE-1

elements specific to cases and controls were identified. Two gene lists from *intra*-genetic LINE-1 sequences, one for cases and another for controls, were used as input for PANTHER gene ontology and pathway analyses. PANTHER analyses showed Bonferroni-corrected statistically significant enrichments for pathways including ‘metabotropic glutamate receptor group I/III’, and ontologies including ‘ion transport’, ‘dendrite’, ‘presynaptic membrane’ and ‘transmembrane receptor protein tyrosine kinase activity’ in TLE cases only. A number of LINE-1 sequences were detected within genes having known associations with seizures/epilepsies among TLE cases and controls; however, the seizure/epilepsy-associated *intra*-genetic LINE-1 sequences had distinct locations between the groups. Each novel LINE-1 is currently being validated and assessed for functional significance. Preliminary results of this study suggest that LINE-1 retrotransposons may contribute to the etiology of some cases of idiopathic TLE.

Disclosures: G.A. Doyle: None. R.J. Buono: None. T.N. Ferraro: None. R. Crist: None. B.C. Reiner: None. G. Arauco-Shapiro: None. R.N. Levinson: None. L.D. Shah: None. W.H. Berrettini: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.04/E41

Topic: B.10. Epilepsy

Support: Regents of the University of California, Initial Complement

Title: Novel genetic tools to assess astrogliosis

Authors: *W. AGNEW-SVOBODA, Y.-C. E. WONG, T. FIACCO, M. RICCOMAGNO
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Abstract: Astrocytes are the most abundant glial cell in the brain, and a critical part of its immune response. When the brain is challenged with an injury or infection astrocytes become reactive. While this response is universal, much remains to be learned about the purpose reactive astrocytes serve. Recently, several genes were identified whose expression in the central nervous system is restricted to reactive astrocytes. Using this knowledge, we have developed a transgenic mouse which expresses Cre in a reactive astrocyte-specific manner (RA-Cre). The RA-Cre mouse is a powerful new tool that will allow the examination of reactive astrocytes across many disease models. To validate this tool, we have characterized the expression of Cre in the mouse line using models of bacterial infection and epilepsy. Using the kainic acid model of epilepsy, the RA-Cre mouse will allow us to determine the impact of reactive astrocytes on disease progression. We will profile the onset, timing and distribution of astrogliosis, and examine how the disease progression is impacted in the absence of reactive astrocytes. These experiments

represent only a small fraction of the possibilities made available by this novel genetic tool. The RA-Cre mouse will allow for studies critical to advance our understanding of reactive gliosis.

Disclosures: **W. Agnew-Svoboda:** A. Employment/Salary (full or part-time):; University of California, Riverside. **Y.E. Wong:** None. **T. Fiocco:** None. **M. Riccomagno:** None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.05/E42

Topic: B.10. Epilepsy

Support: CONACyT (Mexican Council on Science and Technology) Scholarship #381291 to ASR
NINDS 5R01NS097762-02 to PAF

Title: Single maximal electroshock seizures acutely trigger a specific response in hippocampal microglia in mice

Authors: ***A. SEPULVEDA RODRIGUEZ**^{1,3}, **P. LI**^{1,4}, **J. MA**¹, **L. BOZZELLI**^{2,3}, **C. CARLONE**¹, **K. CONANT**^{2,3}, **S. VICINI**^{1,3}, **P. FORCELLI**^{1,3}

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Abstract: Microglia play a central role in the neuroinflammatory response that is characteristic of many epilepsies. A specific pattern of changes in microglial motility and morphology have been described in the mouse hippocampus after severe seizures (Sz) known as Status Epilepticus (SE) (Avignone et al. J Neuro 28(37):9133 2008). SE triggers distinct potent activators of microglial activation (neuronal hyperactivity and neurodegeneration) and results in the development of spontaneous Sz reminiscent of Temporal Lobe Epilepsy (TLE). We aim to characterize the microglial response to abnormal neuronal hyperactivity using Sz induced by in vivo transcorneal Electroconvulsive Shock (ECS) on transgenic reporter mice. Unlike chemoconvulsants, ECS yields reproducible Sz of varying severity without neuronal damage or long-term disruption of neurotransmission. We employ well-established in-slice functional assays of microglial responsive motility to monitor the physiological state of CA1 microglia. P28-P35 female and male CX₃CR1^{eGFP/+} mice were randomized to shock (1 minimal/clonic Sz, 3 min Sz in 1d, 3d with 3 min Sz, or 1 maximal/tonic-clonic Sz) or sham control groups. Confocal fluorescence z- stacks were taken in hippocampal slices every 30s to capture the response of microglial processes in CA1 towards a patch pipette w/ 3mM ATP. Velocity of responsive motility was quantified using Manual Tracking (ImageJ). None of our minimal ECS regimens

affected microglial responsive motility, while a single exposure to maximal ECS significantly enhanced response velocity. As such, we decided to further interrogate the effect of maximal Sz on hippocampal microglia by quantitative morphological analysis (Imaris) and on hippocampal inflammation by ELISA, WB and IF against various pro- or anti-inflammatory markers. We also investigated density and distribution of astrocytes and microglia and observed no changes. Notably, maximal Sz resulted in a significant increase in MCP1, but not in TNF α , when compared to sham shocked controls. Our data suggest that maximal Sz recruit microglial activation pathways reminiscent of the response to SE. In sharp contrast to SE, such Sz are NOT thought to cause hippocampal sclerosis, degeneration nor result in TLE- like spontaneous Sz. In summary, our data suggest that at least part of the SE-induced microglial response can be recapitulated with much less severe acute Sz. These studies could reveal novel biomarkers and therapeutic targets for hippocampal injury, neuroinflammation and epileptogenesis. These data may be additionally relevant for therapeutic uses of ECS, such as treatment of refractory depression.

Disclosures: A. Sepulveda Rodriguez: None. P. Li: None. J. Ma: None. L. Bozzelli: None. C. Carlone: None. K. Conant: None. S. Vicini: None. P. Forcelli: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.06/E43

Topic: B.10. Epilepsy

Title: Sleep quality is not affected by post-seizure latency in the methionine sulfoximine model of epilepsy

Authors: *M. R. BOWER¹, R. B. JOSHI², H. P. ZAVERI³, J. L. GERRARD⁴

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Abstract: The relationship between sleep and epilepsy has been studied extensively, but little is known about the role of post-seizure sleep in establishing long-term changes in neural circuitry. The central role of sleep for the formation of long-term memories involving behaviors (i.e., memory consolidation) motivated the study of long-lasting changes in neural activity following post-seizure sleep. Pre-seizure changes in activity were found to be reactivated during post-seizure sleep, a phenomenon known as Seizure-Related Consolidation (SRC; Bower et al., 2015 & 2017). A potential confound to these studies, however, would be alterations in sleep quality following seizures that could affect the reactivation of seizure-related changes in neural activity, the cellular plasticity machinery that produces long-lasting changes related to post-seizure sleep, or both. For patients undergoing intracranial monitoring for epilepsy, sleep quality measures are

known to change as a function of the length of stay in the ICU, in addition to the well-known difficulties patients experience obtaining quality sleep in an ICU setting. As a step to understanding this problem, the effects of latency of post-seizure rest/sleep were studied in the rodent, methionine sulfoximide (MSO) model of epilepsy. Continuous, high-frequency (30 kHz), intra-cranial recordings were obtained following six spontaneous seizures from one MSO rat. Sleep quality metrics (Joshi et al., 2016) were computed for quiet-rest/sleep periods at different latencies following those seizures. Regression showed no relationship between post-seizure latency and Relative Delta Power ($r^2=0.438$, $p=0.152$), ICU Depth-of-Sleep ($r^2=0.213$, $p=0.357$) or Approximate Entropy ($r^2=0.060$, $p=0.640$). These preliminary results suggest that changes in sleep quality are not dependent upon the latency from the preceding seizure.

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Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.07/E44

Topic: B.10. Epilepsy

Title: Assessing high-frequency oscillation (HFO) rates in EEG signals for seizure prediction

Authors: *D. SEETHARAMA BHAT¹, B. D. KERN², S. D. CABRERA², R. A. ROMERO², S. F. SANDS²

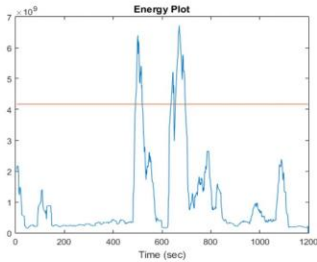
²Electrical Engin., ¹Univ. of Texas at El Paso, El Paso, TX

Abstract: Discovery of high-frequency oscillations (HFOs) as epilepsy biomarkers has prompted new interest in studying the high-frequency content of EEGs to find possible links between epilepsy and HFOs (80 – 800 Hz). In this research, we attempt to strengthen the connection between seizure onset and HFOs by analyzing the prevalence of pathological HFOs during several brain states. We compared the temporal rates of preictal HFOs to rates found in interictal periods.

Analyzed data comprises intracranial EEG signals from the European EPILEPSIAE database, a 180-hour recording from an 8x8 electrode grid annotated with 9 clinical seizures (male patient, age ten) sampled at 2500 Hz, later downsampled to 1250 Hz. To select the most important EEG sensors, we developed a single-channel seizure detector for choosing and ranking channels most likely to be located the closest to the seizure onset zone (SOZ) – the brain region where seizures originate. Our detector is an energy threshold method with the threshold as 3.5 times the standard deviation, see figure 1, and scored for 20 points. From the five highest scored (averaged) channels, see figure 2, we passed twenty-minute segments from preictal periods, interictal periods during slow wave sleep, and while awake through the Montreal Neurological Institute (MNI) HFO detector available in the RIPPLELAB software. Signal patterns were classified as

HFOs if at least four oscillations were clearly visible above background, they had a duration of at least 25 ms, and there was a clear presence of a “power bump” in the time-frequency, see figure 3.

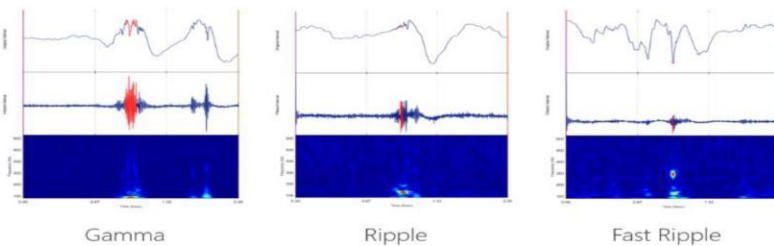
On average, a tenfold increase in the HFO rate from the interictal to preictal period was measured, see figure 4. These brief preliminary results suggest a strong correlation between HFO rate increases and imminent seizure onset, indicating that HFO-based parameters would indeed be viable indicators in seizure prediction methods.



1. Energy Threshold Plot

	1	2	3	4	5	6	7	8
A	37	9	54	30	31	1	44	61
B	55	11	12	29	14	128	104	104
C	18	6	0	25	30	0	74	46
D	73	15	17	11	0	14	86	48
E	10	62	35	0	14	0	15	1
F	43	104	34	0	7	0	0	52
G	54	36	17	5	10	18	8	3
H	36	5	30	15	2	21	38	28

2. Averaged scores for all channels



3. HFO events of interest (gamma 80-100Hz, Ripple 100-250Hz, Fast Ripple >250Hz)

	default	99.99%	99.9%	99%	optimum
events B6	2	2	3	15	15
rate/min	0.1	0.1	0.15	0.75	0.75
events B7	2	2	5	34	34
rate/min	0.1	0.1	0.25	1.7	1.7
events B8	2	2	2	18	18
rate/min	0.1	0.1	0.1	0.9	0.9
events D7	2	3	4	26	26
rate/min	0.1	0.15	0.2	1.3	1.3
events F2	2	3	3	10	11
rate/min	0.1	0.15	0.15	0.5	0.55

	default	99.99%	99.9%	99%	optimum
events B6	2.78	5.44	14.11	41.56	42.56
rate/min	0.36	0.70	1.35	3.40	3.66
events B7	2.56	8.89	21.33	71.33	71.33
rate/min	0.35	0.92	1.77	4.88	4.88
events B8	2.11	3.67	5.67	16.67	16.67
rate/min	0.32	0.65	0.96	2.07	2.07
events D7	2.56	6.67	15.89	49.33	49.33
rate/min	0.34	0.85	1.44	3.54	3.54
events F2	14.78	27.00	45.11	87.67	87.67
rate/min	1.00	1.79	3.01	5.88	5.88

Results

4. An example, using the 99.9% parameter and the F2 electrode it is possible to appreciate a 20 fold increase in HFO's per minute. (Blue table- Awake, Interictal HFO Rates for one 20-minute Segment, Pink table - Average HFO Rates of Preictal Periods)

Disclosures: D. Seetharama Bhat: None. B.D. Kern: None. S.D. Cabrera: None. R.A. Romero: None. S.F. Sands: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.08/E45

Topic: B.10. Epilepsy

Support: NIH NS050229 (NPP)

Title: Specific phosphorylation changes in HCN1 channels during epileptogenesis revealed by mass spectrometry

Authors: F. A. CONCEPCION¹, *N. P. POOLOS²

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Abstract: Previously, we described a loss of surface membrane expression of hyperpolarization-activated, cyclic nucleotide-gated type 1 (HCN1) channels following status epilepticus (SE), contributing to chronic loss of I_h (the current mediated by HCN channels) in a rat model of epilepsy (Jung et al., 2010, 2011). We also showed that HCN1 channel surface membrane expression was modulated by phosphorylation (Williams et al., 2015). We therefore hypothesized that changes in phosphorylation at individual HCN1 phosphosites occur in both the acute and chronic stages of epileptogenesis, the development of epilepsy after a brain insult. We collected CA1 hippocampal tissue from male Sprague Dawley rats one hour after the onset of pilocarpine-induced SE (1 hr post-SE), and from their age-matched naïve controls (n = 12 each), as well as from chronically epileptic rats (6-8 weeks post-SE, n=8). After HCN1 enrichment by immunoprecipitation and trypsin in-gel digestion, the samples were analyzed by mass spectrometry. Six HCN1 phosphosites were detected in 100% of samples. Of these phosphosites evaluated at 1 hr post-SE, a statistically significant phosphorylation change was seen only at S891: a 50% decrease compared to control (1 hr post-SE phosphorylation level $11.5 \pm 2.99\%$; control $22.8 \pm 3.18\%$; $p=0.016$). Loss of phosphorylation at S891 was maintained in tissue from chronically epileptic rats, with a 58% decrease in epilepsy (chronic: $9.64 \pm 4.06\%$). Also seen in chronic epilepsy was a 49% increase in phosphorylation at S791 (chronic $33.1 \pm 3.51\%$; control $22.1 \pm 2.52\%$; $p=0.018$). Phosphorylation levels at the other phosphosites in both acute and chronic conditions were unchanged. These data represent a novel survey of HCN1 phosphorylation sites. During epileptogenesis, persistent dephosphorylation occurs at S891, a residue located 20 amino acids from the carboxyl end of the HCN1 protein, and a potential region of interactions with accessory proteins. This dephosphorylation near its carboxyl terminal may mediate HCN1's lowered surface expression during epileptogenesis. Future experiments are needed to validate the role of phosphorylation changes at S891 and S791 on the function of HCN1 channels.

Disclosures: F.A. Concepcion: None. N.P. Poolos: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.09/E46

Topic: B.10. Epilepsy

Support: AES Grant 411837
R56NS096234

Title: Altered levels of triggering receptor expressed on myeloid cells 2 (trem2) in epilepsy

Authors: *S. K. JOHNSON, A. L. BREWSTER
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Abstract: A single episode of status epilepticus (SE) can result in the development of epilepsy. SE triggers pathological remodeling of the hippocampus that is associated with neuronal loss and activation of microglia, the brain's immune cells and professional phagocytes. While chronic inflammatory microglia are widely known to aggravate seizures, less is known about the status of their phagocytic properties. Recently, we reported that the microglial phagocytic receptor Trem2 is downregulated in human drug-resistant epilepsy. This is important because loss-of-function mutations in Trem2 occur in Nasu-Hakola, a disorder associated with bone cysts, neurological decline, and seizures. This suggests the possibility that altered levels of Trem2 may be a candidate mechanism underlying SE-provoked epileptogenic hippocampal changes. Therefore, to understand a potential role for Trem2 the objective of this study was to characterize the effects of SE on microglial Trem2 expression in the hippocampus. One hour of SE (Racine scale level 5) was induced with pilocarpine and stopped with diazepam in rats. Controls were given saline. To assess Trem2 expression in microglia two cohorts of SE and control animals were sacrificed at 2wks post SE. All animals were perfused with saline. One cohort was post-fixed for histology using antibodies against IBA1, Cd11b, and Trem2 (n=3-5 /group). In the second cohort, hippocampi were dissected and processed for flow cytometry (FC) using antibodies against CD45, Cd11b, MHCII, and Trem2 (n=3-4/group). Histology revealed a significant increase in the number of IBA1 positive microglia in hippocampi of the SE group compared to controls (p<0.05). Immunostaining revealed weak Trem2 staining in control hippocampi compared to a more robust signal colocalized with IBA1/Cd11b-positive microglia in the SE group. FC analysis confirmed that hippocampi of SE rats had an increased population of Cd11b/CD45 positive microglia compared to the controls (p<0.05). Within this population we found increased numbers of MHCII and decreased Trem2 positive microglia in the SE group compared to the control (p<0.05). These data suggest that SE-induced microgliosis at 2wks post SE is associated with a high population of MHCII positive microglia and a lower population of phagocytic Trem2 positive microglia. Together these data suggest that at this time point the

hippocampus contains a heterologous population of microglia with different functions (inflammatory/phagocytic) that may comprise distinct biochemical and functional properties that contribute to the neuropathology of epilepsy.

Disclosures: S.K. Johnson: None. A.L. Brewster: None.

Poster

039. Epilepsy

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Program #/Poster #: 039.10/E47

Topic: B.10. Epilepsy

Support: NIH R01 NS095842

Title: Effect of dorsal raphe serotonin neuron stimulation on post-ictal EEG suppression and arousal in mice

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Abstract: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in refractory epilepsy patients. While the exact etiology of SUDEP is unknown, it is thought that post-ictal arousal impairment may contribute. Seizures often result in post-ictal generalized EEG suppression (PGES). PGES may correlate with decreased arousal following a seizure. PGES duration has been associated with increased SUDEP risk. Seizures cause a rise in CO₂ and also dysregulate serotonin (5-HT). 5-HT influences sleep/wakefulness. 5-HT neurons in the dorsal raphe nucleus (DRN) are CO₂ chemosensors. Our lab has shown these neurons are important in CO₂ induced arousal, and can be reliably stimulated with CO₂-enriched artificial cerebrospinal fluid (aCSF). We hypothesized that PGES may be an electrographic marker for impaired arousal, and that increasing serotonergic tone by stimulating DRN 5-HT neurons with CO₂-enriched aCSF (acidosis), or treating animals with 5-HT or a selective serotonin reuptake inhibitor (SSRI) might reduce PGES duration. C57BL/6J mice (12 male/10 female; 8-12 wks; Jackson Labs, Bar Harbor, ME) were implanted with EEG and EMG electrodes, a bipolar stimulating electrode in the basolateral amygdala (in mm from bregma: AP: -1.3; ML: -2.8; DV: -4.7), and a microdialysis cannula directed toward the lateral ventricle (AP: -0.4; ML: -1.3; DV: -1.7) or DRN (AP: -5.97; ML: ±0; DV: -4; 20° posterior angle). After surgical recovery, animals underwent afterdischarge threshold determination, and were kindled with the threshold current (120-500 μA; 1 s train; 1 msec biphasic square waves; 60 Hz; 2x/day) until three consecutive Racine 4-5 seizures were observed. Once kindled, animals underwent seizure inductions during wake/sleep following treatment with DRN acidosis (45 μl/min; 10 min before seizure), 5-HT (1

or 3 mM; 45 μ l/min; *icv*; 30 min before seizure), or citalopram (SSRI; 20 mg/kg, *ip*; 30 min before seizure). Control mice received normal aCSF perfusions, or *icv* or *ip* saline, respectively. To investigate arousability during PGES, animals underwent seizure inductions during wake/sleep and were challenged with hypercapnia (7% CO₂/21% O₂/72% N₂) or room air (21% O₂/79% N₂) for 60 s at 0 or 5 min after seizure end. All implant placements were verified histologically. DRN acidosis, *icv* 5-HT, and *ip* citalopram all decreased PGES length with no effect on seizure length. PGES following kindled seizures correlated with reduced CO₂-induced arousal. These data suggest that treating with serotonergic agents may reduce EEG suppression and reduced arousal following a seizure. Further work will be required to determine whether this will also lead to reduced SUDEP risk.

Disclosures: A. Petrucci: None. K. Joyal: None. G.F. Buchanan: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

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Program #/Poster #: 039.11/E48

Topic: B.10. Epilepsy

Support: NIH Grant F99 NS105211
NIH Grant R21 NS093364
CURE Challenge Award
Lily's Fund Spark Award

Title: Elucidating the role of enhancer of zeste homolog 2 (*ezh2*) in epilepsy

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Abstract: Epilepsy is the fourth most prevalent neurological disorder with an incidence of 1 in 26 individuals. While a number of anti-convulsants exist to treat single seizure episodes, no anti-epileptogenic drugs are currently available to stop disease progression. Epileptogenesis is associated with alterations in synaptic plasticity, cell death, inflammation, and a reduction in seizure threshold. To investigate which transcriptional regulators are responsible for these outcomes, we analyzed a set of dentate granule cell expression profiles laser captured after Status Epilepticus (SE) in three rat seizure models: pilocarpine, kainic acid, and self-sustained SE. Our analysis predicts that increased Enhancer of Zeste Homolog 2 (EZH2) function is a principle driver of gene expression changes during epileptogenesis across epilepsy models. This is significant because EZH2 plays an important role as part of the Polycomb Repressive Complex

during development, where it epigenetically and stably silences genes. In this study, we have used the kainic acid mouse model to test this prediction and characterize the molecular function of EZH2 after SE. We have found that EZH2 protein levels are robustly induced after SE, peaking at two days with a 6.3-fold up regulation and remaining increased out to five days. We also provide evidence that this increase is functional, by observing a down regulation in EZH2 target gene expression as much as 10 days after SE. Through immunofluorescence, we demonstrate that increased EZH2 levels are localized to hippocampal neurons. Administration of the small-molecule EZH2 inhibitor UNC1999 to epileptic mice significantly increases seizure burden, suggesting a protective rather than pathological role for EZH2 upregulation. We validate the presence of UNC1999 in the brain by performing LC/MS on UNC1999 and vehicle treated hippocampal tissue. With these data, we are the first lab to show that UNC1999 crosses the blood-brain-barrier after systemic delivery.

Our aim is to determine the mechanism by which EZH2 becomes up regulated after SE and determine if exogenous delivery of EZH2 is sufficient to decrease seizure activity after the on-set of epileptogenesis. This project is one of the first to characterize a role for EZH2 in epileptogenesis and may foster the development of EZH2 agonists as potential anti-epileptogenic drugs. Deciphering the role of EZH2 will bring novel insight into epileptogenesis and shed light on novel strategies for treating one of the most common neurological disorders today.

Disclosures: N.N. Khan: None. B. Schoenike: None. T. Basu: None. G. Rodriguez: None. C. Sindic: None. M. Johnson: None. E. Wallace: None. R. Maganti: None. R.J. Dingledine: None. A.S. Roopra: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.12/E49

Topic: B.10. Epilepsy

Title: Adult born dentate granule neurons show accelerated maturation in a transgenic mouse model of adult-onset spontaneous epilepsy

Authors: M. S. HOSSAIN, A. POUGH, K. KOROMA, *C. ISGOR

Charles E. Schmidt Biomed Ctrr, Florida Atlantic Univ. Charles E Schmidt Col. of Med., Boca Raton, FL

Abstract: Dentate granule neurons (DGNs) of the hippocampus gate neuronal information coming into the hippocampus, and are hypothesized to play a role in blocking propagation of seizure hyperexcitability. Cortical spread of hyperexcitability is associated with tonic/clonic seizures with loss of consciousness. It is not well understood how adult born DGNs contribute to seizure prone circuits or how seizure neuro-environment can impact the maturation of DGNs. In

this experiment we used a transgenic mouse model that over expresses the brain-derived neurotrophic factor in the forebrain under the CAMKIIa promoter that develops adult-onset spontaneous seizures (termed TgBDNF mice). TgBDNF mice allow for studying progressive synaptic changes that are pro-epileptic and can be readily separated from seizure-induced changes. Our laboratory previously showed that a subset of these mice (~60%) develops spontaneous seizures that are elicited by brief tail suspension and cage agitation at ~4-5 months of age and more mice become epileptic with age. We reported expansion of hippocampal mossy fiber (MF) terminal fields in this strain prior to seizures (2-3 months of age), and increased dentate molecular layer volume. At later, seizure-prone ages (6-8 months) further MF expansion is observed, and granule cell numbers are increased. We also showed that mature hippocampal granule neurons have more dendritic spines both in pre-seizure (8-12 wks) and seizure-prone (6-7 months) ages compared to control mice. These progressive changes suggest that prior to motor seizures, excess BDNF is remodeling dentate circuitry, a process that continues with age. In the current study we assessed the maturation of newly born granule cells under BDNF rich local environment in pre-seizure and seizure prone ages. We bred epileptic strain of mice with a strain that transiently (3 wks post mitosis) expresses GAD67-GFP in the adult born DGNs to assess dendritic development of incoming neurons. Our data show that newborn DGNs mature faster in seizure prone mice evidenced by increased dendritic complexity and spinogenesis. These effects were distributed heterogeneous between suprapyramidal and infrapyramidal GC populations. These findings suggest newborn DGNs could critically enhance net excitability of hippocampus and promote seizure prone circuits.

Disclosures: M.S. Hossain: None. A. Pough: None. K. Koroma: None. C. Isgor: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.13/E50

Topic: B.10. Epilepsy

Title: The effect of cannabidiol on microglial function and receptor expression in an epilepsy mouse model

Authors: *T. R. VICTOR¹, J. C. NISSEN⁴, M. W. ELMES², D. G. DEUTSCH², S. E. TSIRKA³

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Abstract: Epilepsy is a chronic disorder characterized by abnormal brain cell activity leading to recurrent, unprovoked seizures. Pharmacological therapies are commonly used for the treatment of epilepsy, although nearly 30% of patients do not respond to current medications. This

highlights the need for new drug targets and treatments. Many recent studies have centered on the use of cannabidiol (CBD) to treat epilepsy. Early use of CBD, a non-psychotropic component of *Cannabis sativa*, is reported to lessen the severity of experimentally induced seizures in animals and to suppress neuroinflammation in culture. Although CBD has been shown to increase intracellular levels of anandamide, an endogenous cannabinoid, its complete mechanism of action is still poorly understood. Our previous studies have shown that microglia, the immune cells of the central nervous system (CNS), are important mediators of seizure severity. Microglial ability to modulate seizures has been linked to the activation of Toll-like receptors (TLRs). TLRs play important roles in pathogen recognition and inflammation. Microglia also act as modulators of neurogenesis and synaptogenesis, contributing to the refinement of functional neuronal circuits. We postulate that CBD modulates the activation of microglial cells to exert beneficial effects in the brain. In this study, we evaluate the effects of CBD on inflammation and microglial receptor expression invitro and in vivo.

Disclosures: T.R. Victor: None. J.C. Nissen: None. M.W. Elmes: None. D.G. Deutsch: None. S.E. Tsirka: None.

Poster

039. Epilepsy

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Topic: B.10. Epilepsy

Support: NIH-RO1-NS036692
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NIH-RO1-NS052634

Title: Matrix metalloproteinase-mediated degradation of perineuronal nets contributes to tumor-associated epilepsy

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Abstract: Glioblastoma, a grade IV brain tumor is the most malignant form of tumors and often present with seizures. Previously we have shown that glutamate released from glioma cells owing to the increases expression of cystine/glutamate transporter System xc (SXC) leads to the generation of epileptic seizures in a human glioma injected mice model. Glioma cells are also known to release an array of molecules including matrix-degrading enzymes to facilitate their spread in invasion to distant brain regions. Extracellular matrix has emerged as an important regulator of neuroglia functions and implicated in several CNS disorders including epilepsy. In

present study, we explored the possibility of glioma secretome mediated alterations in extracellular matrix, especially the highly negatively charged lattice like perineuronal nets, which surround GABAergic interneurons in mouse model of glioma-associated epilepsy. We observed a widespread decrease in the numbers of PNNs and structural disintegration of those remaining in peritumoral cortex of glioma-injected brains. Peritumoral cortex also exhibited reactive astrogliosis. PNNs components are potential substrates for matrix degrading enzymes including MMPs, and glioma and/or reactive astrocytes can be the prime source. We performed in-situ zymography to explore the correlation of PNN degradation and activity of MMPs in the peritumoral cortex. Our data show high gelatinase activity in glioma cells but not in reactive astrocytes suggesting glioma cells as the main source of PNN degrading MMPs. To further confirm that MMPs are the primary mediators of PNN degradation, we injected a broad-spectrum MMP inhibitor GM6001, in glioma-injected mice and observed significant reduction in MMPs activity and substantial rescue of PNNs numbers and structural integrity. Our data suggest that PNN disintegration in glioma-associated epilepsy is mediated by MMPs released from glioma cells and rescuing the integrity of PNNs by inhibiting MMPs can potentially overcome the dysfunction of PNN enwrapped GABAergic interneurons in various CNS disorders.

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Poster

039. Epilepsy

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Program #/Poster #: 039.15/F1

Topic: B.10. Epilepsy

Support: NHMRC (Australia) Project 1050832

Title: Diverse effects of a kindling model of epilepsy on different inhibitory cell types in the piriform cortex

Authors: J. J. ROBERTSON, *J. M. BEKKERS
John Curtin Sch. Med. Res., Acton, Australia

Abstract: The primary olfactory (piriform) cortex has been shown to be involved in the generalization of epileptic seizures, but the mechanism is unclear. A small number of studies suggest that epilepsy causes cell death in the piriform cortex. Previous work in our laboratory has identified different classes of inhibitory neurons in the piriform cortex that can be identified using immunohistochemical markers. However, the effect of epilepsy on these different classes has not previously been investigated. The current study aimed to compare the effect of electrical kindling on different inhibitory cell types in the piriform cortex. Experiments used transgenic

mice that express green fluorescent protein (GFP) in GABAergic neurons (GAD67-GFP mice). Mice (P24-26) were kindled using an olfactory bulb electrical stimulation protocol, and seizures were confirmed using electrocorticograms (ECoGs) with video verification. Kindled mice were compared to age-matched control and sham mice. Animals were perfusion-fixed and 100 μm thick slices prepared. Slices were immunohistochemically processed to detect parvalbumin, calbindin, vasoactive intestinal peptide and somatostatin, allowing for identification of different classes of interneurons. Sections were imaged using a Nikon confocal microscope and cells counted using a custom ImageJ macro. We found a 13% overall reduction in the number of inhibitory neurons in the piriform cortex in the kindled mice compared to the sham and control ($p < 0.01$, $n = 22614$ neurons, $n = 216$ slices, $n = 12$ mice). Regular-spiking multipolar cells were reduced in density in kindled ($5.11 \pm 0.68 \times 10^3$ neurons/ mm^3) compared to both control ($8.78 \pm 0.94 \times 10^3$ neurons/ mm^3) and sham mice ($7.62 \pm 0.74 \times 10^3$ neurons/ mm^3) ($p < 0.001$). We also found a reduction in the density of bitufted cells in the kindled ($1.59 \pm 0.50 \times 10^3$ neurons/ mm^3) compared to control mice ($6.3 \pm 1.63 \times 10^3$ neurons/ mm^3) ($p < 0.001$), however the sham mice showed a similar reduction ($0.81 \pm 0.27 \times 10^3$ neurons/ mm^3) ($p > 0.05$ compared to kindled, $p < 0.001$ compared to control). Layer 2 neurogliaform cells showed a similar pattern of change to the bitufted cells. In contrast, the density of horizontal cells, neurogliaform cells in layers 1 and 3, and fast-spiking multipolar cells, remained unchanged ($p > 0.05$). This study provides the first rigorous characterization of the effect of epilepsy on inhibitory cell types in the piriform cortex, and demonstrates that the effect of kindling appears to be cell-type specific. Our results may provide mechanistic insight into seizure generalization through the piriform cortex and suggest therapeutic targets.

Disclosures: J.J. Robertson: None. J.M. Bekkers: None.

Poster

039. Epilepsy

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Program #/Poster #: 039.16/F2

Topic: B.10. Epilepsy

Title: Changes in structure and function of thin, hippocampal axons in epileptic mice

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Abstract: Communication between neurons in the mammalian cortices rely on propagation of action potentials in extremely thin unmyelinated axons making *en passant* synapses with a very large number of other neurons. Such axons comprise 50% of the volume and form 85% of all

synapses in cortex. Knowledge about the pathology of thin axons would be important for all cortical diseases but is particularly obvious in epilepsies because axons are the most excitable elements of cortex, and control almost all release of the excitatory transmitter glutamate.

Rationale: Simple simulations show that intra-axonal diffusion and action potential propagation is sensitive to differences in thin-axon morphology even within the normal range of morphologies. To identify average differences in morphology that may influence the function of thin axons we investigated axons in the hippocampi from 12 wild-type (WT) and 15 epileptic mice (*Scn1a*^{+/-} mouse model of Dravet syndrome). Axonal function was studied by utilizing techniques proven to be useful for functional testing of peripheral neuropathies and we tailored them to the conditions in cortex. **Structure:** To detect average changes in structure, individual thin axons were labelled with lipophilic dye (DiI). We measured inter-bouton intervals (IBI) and fluorescent intensity ratio (FIR) between boutons and shafts. We found that the epileptic mice had 25% higher FIR and 26% higher coefficient of variation of IBI compared with wild-type mice (ages 4- 5 months). The effects of such morphological differences on diffusion and propagation were explored by simulations. **Function:** Peripheral thin unmyelinated C-fibers have been shown to conduct slower when activated repeatedly. Interestingly, they slow less in humans with some pain-related diseases. We therefore quantified activity-dependent slowing in the WT and epileptic mice. We found that WT slowed 38 ± 2.5 % and epileptic mice only 29 ± 2.5 % at ~8 Hz stimulation. We also found that activity-dependent slowing in thin cortical axons was sensitive to blockers of the Na-K-pump, suggesting that the epileptic mice had higher levels of the pump. Since thin-axon morphology theoretically influences their function and is relatively stable over at least several months, the systematic morphological differences we observed between normal and epileptic mice may contribute to some of the features of epilepsies, like recurrence and treatment resistance.

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Poster

039. Epilepsy

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Program #/Poster #: 039.17/F3

Topic: B.10. Epilepsy

Support: New York State Office of Mental Health
Pyramid Biosciences, Inc.

Title: Trk inhibition in a new experimental model of seizures and spreading depolarization/spreading depression

Authors: *Y.-L. LU¹, J. S. SPROUSE², H. E. SCHARFMAN^{3,4}

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Abstract: Spreading depolarization or depression (SD) is a large, often sudden depolarization of cortical neurons that has been proposed as an underlying mechanism for migraine and seizures. We hypothesized that there was an important role of the neurotrophin brain-derived neurotrophic factor (BDNF) acting at TrkB receptors and developed a new experimental model to test this hypothesis in rodent hippocampal slices. This experimental model provides the first opportunity to study SD as well as simulate epileptogenesis and do so in a slice chamber amenable to whole-cell recording. Slices were made using standard methods (350 μ m-thick, horizontal plane, dissection in sucrose-based artificial cerebrospinal fluid (aCSF)) and put in a holding chamber in sucrose aCSF with temperature gradually increasing to 35°C and maintaining at 35°C for 45 min. Slices were kept in the holding chamber at room temperature in sucrose aCSF until being transferred to the recording chamber with a high flow rate (6-7 mL/min) of NaCl-based aCSF (0 mM Mg²⁺/5 mM K⁺) flowing above and below the slice (Warner, RC-27LD). The recordings were acquired in area CA3. We observed ictal-like events in all rat slices (5 slices, 3 rats) and 50% of mouse slices (11/22 slices, 16 mice). SD events were only observed in mouse slices (18/22 slices), and the first SD or ictal-like event developed at 31.2 ± 1.9 min after 0 mM Mg²⁺/5 mM K⁺ aCSF exposure (range: 19.0-55.8 min; n = 22 slices, 16 mice). These events were delayed 10.5 ± 2.3 min by 500 nM K252a (pre-treatment of K-252a for 15 min in the holding chamber and continuous K-252a exposure in the recording chamber) compared to vehicle (0.001% dimethyl sulfoxide; 8 slices from 7 mice for each group; unpaired t-test, p = 0.0076). We conclude that Trk inhibition delays but does not block SD and ictal-like events. These results suggest that this new *ex vivo* model could be beneficial to understand the mechanisms and roles of neurotrophins and Trk receptors underlying migraine and seizures.

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Poster

039. Epilepsy

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Program #/Poster #: 039.18/F4

Topic: B.10. Epilepsy

Support: RO1NS082046

Title: Anatomical and morphological evidence showing active hippocampal dentate granule cells are mature cells

Authors: *S. A. PARK¹, D. COULTER^{1,2,3}

¹Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA; ²Pediatrics, Children's Hosp. of Philadelphia, Philadelphia, PA; ³Neurosci., The Univ. of Pennsylvania, Philadelphia, PA

Abstract: The hippocampus is a critical mediator of spatial learning and navigation. The dentate gyrus contributes to this function through its sparse activation properties, which aids in distinguishing between similar cortical inputs (pattern separation). With 2-photon imaging of awake, behaving animals navigating a virtual environment, we observed that only a small number of dentate granule cells (DGCs) are active. Previous studies indicate that active DGCs (aDGCs) are adult-born DGCs, not mature DGCs. Interestingly, our data suggest that aDGCs are primarily mature. To label aDGCs in vivo, we used fos-TRAP (targeted recombination in active populations) transgenic mice, crossed to tdTomato reporter mice following exposure of mice to an enriched environment and 4-hydroxytamoxifen injection. In active neurons of fosTRAP mice, the fos promoter drives expression of CreERT, which, in the presence of tamoxifen, drives tdTomato reporter expression. We imaged aDGCs and inactive DGCs (iDGCs) from hippocampal slices prepared from these same mice and performed extensive anatomical and morphological analyses comparing aDGCs and iDGCs. As expected, fosTRAP labeled aDGCs were sparse: on average, 7.2 cells were labeled with tdTomato per dentate blade in a given slice. To explore whether aDGCs are adult-born, mature, or both, we compared and observed a difference in the distribution of aDGC locations within the granule cell layer (GCL) from fosTRAP mice to the distribution of DGC locations within the GCL from Thy1-GCaMP6s mice (K-S test, $p < 0.0001$). Surprisingly, our results show a disproportionate population of aDGCs to be located away from the subgranular zone, beyond the inner third of the GCL where adult-born DGCs are expected to be found, implying that a large proportion of aDGCs are mature and have not retired. Adult-born DGCs have shorter dendrites and less branching than mature DGCs. However, our morphology data show that aDGCs compared to iDGCs have longer maximal dendrite lengths ($256.0 \pm 7.3 \mu\text{m}$ vs. $231.4 \pm 5.3 \mu\text{m}$; unpaired, 2-tailed t-test, $p = 0.0139$) and a trend towards greater branching based on Sholl analysis (2-way ANOVA, $p = 0.0973$) and Shreve branch order analysis (13.67 ± 1.61 vs. 10.64 ± 1.62 ; unpaired, 2-tailed Mann-Whitney test, $p = 0.0698$), further supporting that mature DGCs are active. Additionally, the intrinsic properties between aDGCs and iDGCs have an inverse relationship from expected values, reinforcing the idea that aDGCs are not adult-born DGCs. Combined, these results suggest that aDGCs are primarily mature DGCs, challenging the current notion that adult-born DGCs are the aDGCs.

Disclosures: S.A. Park: None. D. Coulter: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.19/F5

Topic: B.10. Epilepsy

Support: EU project 642881

Title: Acute reduction of the extracellular trans-synaptic protein LGI1 increases network excitability

Authors: *E. LUGARA¹, E. CHABROL², G. LIGNANI³, M. C. WALKER⁴

¹UCL Inst. of Neurol., London, United Kingdom; ²UCL, London, United Kingdom; ³UCL Inst. of Neurolgy, London, United Kingdom; ⁴UCL, Inst. of Neurolgy, London, United Kingdom

Abstract: LGI1 (Leucine Rich Glioma Inactivated 1) is a secreted trans-synaptic protein which interacts presynaptically with Kv1.1 potassium channels and ADAM23, a membrane-anchored protein with no catalytic effect. Postsynaptically, LGI1 influences AMPA and NMDA receptors through a direct link with the ADAM22 adhesion protein. Mutations in the gene encoding LGI1 lead to temporal lobe epilepsy in humans and animal models. Autoantibodies against LGI1 have been detected in the serum of adult patients with limbic encephalitis and seizures.

Although LGI1 is strongly implicated in the generation and spread of seizures in genetic and developmental forms of epilepsy, the mechanisms by which LGI1 affects neuronal networks are still debated. My aim is to determine how an acute reduction of LGI1 in the brain leads to epilepsy in rodent models.

For this purpose, I chose and validated a silencing RNA (shRNA) against LGI1. In neuronal cultures and in *ex vivo* granule cells, shRNA against LGI1 increased neuronal firing. Local field potential (LFP) of *ex vivo* slices after injection of shRNA-LGI1 in the hippocampus, revealed an increase in the facilitation of mossy fibers to CA3 pyramidal cell neurotransmission. Application of Kv1 family blocker, alpha-dendrotoxin, occludes the increased facilitation in shRNA-LGI1 injected mice.

My results indicate that an acute reduction in LGI1 is sufficient to increase neuronal network excitability. Specifically, acutely decreasing LGI1 protein affects synaptic excitability and short-term plasticity in DG-CA3 hippocampal circuitry. shRNA against LGI1 can be successfully used as a tool to dissect the role of this protein in specific local circuits.

Disclosures: E. Chabrol: None. G. Lignani: None. M.C. Walker: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.20/F6

Topic: B.10. Epilepsy

Support: NSERC

CONACyT

Title: Altered glutamatergic synaptic transmission associated with early life inflammatory challenge-induced adult seizure vulnerability

Authors: *C. D. GÓMEZ MARTÍNEZ, M. L. LEWIS, Q. J. PITTMAN

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Abstract: Increasing evidence has shown that early life inflammatory-stress can influence seizure susceptibility in later life. Most experimental studies however, have not investigated the importance of sex-specific differences and the underlying mechanisms are still missing. Here, C57/BL6 mice were bred in house, and female and male pups from multiple litters were injected with lipopolysaccharide as the immune-activation paradigm (LPS, 100 µg/kg *i.p.*) or vehicle control (saline solution) at postnatal day 14 (p14). Then, seizure threshold was assessed in response to pentylenetetrazol (1% solution, *i.v.*) in adulthood (p60-70). We found that mice injected with LPS displayed ~25% lower seizure threshold compared with controls. Moreover, both female and male mice injected with LPS showed similar increases in seizure susceptibility, suggesting altered brain excitability is not sex-dependent in these mice. Whole-cell recordings revealed that inflamed CA1 hippocampal pyramidal neurons from adult mice of both sexes displayed spontaneous EPSC frequency approximately twice of that of controls, but amplitude was unchanged. This was associated with an increased probability of glutamate release to Schaffer collateral stimulation. No significant synaptic alterations were observed in adolescent (p35-45) female and male mice. Our new findings demonstrate that early life inflammatory insult leads to long term increased excitability in adult female and male mice hippocampus associated with changes in glutamatergic synaptic transmission. These alterations may contribute to enhanced vulnerability of the brain to subsequent pathological challenges such as epileptic seizures.

Disclosures: C.D. Gómez Martínez: None. M.L. Lewis: None. Q.J. Pittman: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.21/F7

Topic: B.10. Epilepsy

Support: University of Otago Scholarship
BHRC travel bursary

Title: Investigating mechanisms underlying absence epilepsy using DREADD technology to silence microcircuits within the cortico-thalamic-cortical network

Authors: S. PANTHI, *B. LEITCH

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Dunedin, New Zealand

Abstract: Absence epilepsy is a genetic, generalized, non-convulsive form of epilepsy and is the most common type of childhood epilepsy. The hallmark of absence seizures is concomitant spike-wave discharges (SWDs) measuring 2.5-4 Hz on an EEG. Patients can have hundreds of seizures per day leading to behavioural disorders, poor academic achievement and increased risk of physical injury in some cases. Despite advances in pharmacological therapies, anti-epileptic drugs (AEDs) fail to control the seizures in one-third of patients or induce intolerable adverse effects in others. Hence, there is an urgent need for more targeted approaches for the treatment of absence epilepsy that are patient specific. This requires an understanding of seizure generation at the cellular and molecular level. It has been established that absence seizures arise from disturbances in the cortico-thalamo-cortical (CTC) network. Within this network, feed-forward inhibition (FFI) is essential to prevent runaway excitation and is mediated by fast spiking parvalbumin-containing (PV⁺) inhibitory interneurons in the somatosensory cortex and the reticular thalamic nuclei (RTN). We previously reported that defects in the activation of PV⁺ interneurons in the stargazer model of absence epilepsy could lead to dysfunctional FFI, which may alter CTC network oscillation contributing to seizure generation. Hence, feed-forward inhibitory interneurons might be potential targets for treatment of absence epilepsy. In this study, we used DREADD technology to control the activity of PV⁺ interneurons using PV-Cre x G_i-DREADD floxed mice to test the hypothesis that disruption of FFI is one of the mechanisms through which SWDs are generated. We first confirmed the exclusive expression of DREADD receptors in the PV⁺ interneurons of the SSCortex and RTN via confocal fluorescence microscopy. EEG traces were recorded before and after injection of Clozapine-N-Oxide (CNO) to investigate if silencing PV⁺ interneurons leads to the generation of SWDs. Bursts of paroxysmal oscillatory activity with the characteristics of SWDs were induced after injection of CNO either peripherally (i.p.) or focally (into SSCortex). The onset of discharges was 41.85 ± 3.13 min (i.p. injection) and 14.13 ± 7.47 min (focal injection). Simultaneous EEG and video recording showed that the bursts of paroxysmal oscillatory activity were associated with behavioural arrest. However, CNO injection into non-DREADD controls showed no seizure activity or behavioural arrest. These data suggest that disruption of FFI could be one mechanisms through which SWDs are generated. Further investigations can guide improved treatment strategies.

Disclosures: S. Panthi: None. **B. Leitch:** None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.22/F8

Topic: B.10. Epilepsy

Title: Spillover-induced shifts in the contribution of synaptic and extrasynaptic GABA-A receptors after brief convulsant stimulation favors slowing and synchronization of hippocampal networks

Authors: *D. E. NAYLOR^{1,2}

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Abstract: Seizure onset often is marked by fast-rhythmic activity associated with a rapid and enduring loss of synaptic inhibition as measured by paired-pulse inhibition. After several seconds, slow synchronous 3 - 6 Hz activity emerges with summated action-potential 'spike' followed by the slower synaptic potential mediated 'wave', and this persists for approximately one minute before incremental slowing progresses to seizure termination with a prolonged inhibitory post-ictal phase. Postsynaptic GABA-A receptors containing gamma2 subunits mediate phasic inhibitory currents in hippocampal granule cells in response to brief high concentration transmitter release and rapidly desensitize to low-level tonic or brief hi-frequency pulsatile GABA exposure. Conversely, extrasynaptic GABA-A receptors containing delta subunits are largely non-desensitizing, have greater GABA affinity, and are responsible for tonic inhibitory currents in response to mostly stable low concentrations of extracellular GABA. It is uncertain how conditions can influence GABA spillover to extrasynaptic sites and impact the spatio-temporal profile of GABAergic inhibition and influence circuit behavior. To probe this, computational models were developed and optimized to fit phasic/IPSC, tonic, and multi-synaptic evoked currents and showed that high-frequency activity rapidly desensitizes postsynaptic receptors in a frequency-duration dependent manner that, along with estimated 1-3 micromolar activity-induced increases in GABA, contributes to persistent losses of paired-pulse inhibition. In addition, prolonged hi-frequency stimulation promotes GABA spillover to a relatively few extrasynaptic delta subunit-containing receptors (~ 4 per each synapse vs. 36 postsynaptic gamma subunit-containing receptors per synapse), but the extrasynaptic contribution can account for up to 60% of the charge transfer of an evoked inhibitory response, prolonging and broadening the spatial extent of synaptically-released GABA favoring network slowing. In summary, evidence is provided for the evolution of seizures from a phase of fast-rhythmic activity that progresses to a phase of slowing synchrony that depends on a dynamic shift of activation from synaptic to extrasynaptic GABA-A receptors. Identifying the components that shape network dynamics during seizure onset and evolution should suggest new therapeutic approaches that target specific types of pathophysiological circuit behavior.

Disclosures: D.E. Naylor: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 039.23/F9

Topic: B.10. Epilepsy

Title: Binding mode and physiological role of epilepsy-related ligand/receptor LGI1-ADAM22 complex based on structural analysis

Authors: *Y. MIYAZAKI^{1,2}, A. YAMAGATA³, N. YOKOI², Y. FUKATA², S. FUKAI³, M. FUKATA²

¹Okazaki, Japan; ²Div. of Membrane Physiology, Natl. Inst. for Physiological Sci., Okazaki, Japan; ³Inst. for Quantitative Biosciences, The Univ. of Tokyo, Tokyo, Japan

Abstract: LGI1 is a neuronal secretory protein and its mutations were reported in patients with a familial epilepsy, autosomal dominant lateral temporal lobe epilepsy (ADLTE). LGI1 functions as a ligand for ADAM22 or ADAM23, epilepsy-related transmembrane proteins. Previously, we have reported that loss of LGI1-ADAM22 interactions causes abnormal synaptic transmission and epileptic seizures in mice. However, the structural basis and physiological role of LGI1-ADAM22 complex formation remain unclear. Here, we report the crystal structure of human LGI1-ADAM22 complex, revealing a 2:2 heterotetrameric assembly mediated by LGI1-LGI1 interaction. LGI1 binds to ADAM22 and ADAM23 in a similar manner. Interestingly, an ADLTE mutation, which does not affect either the secretion or the ADAM22 binding, is located in the LGI1-LGI1 interface and disrupts the higher-order assembly of the LGI1-ADAM22 complex in vitro and in vivo, resulting in epilepsy. These studies support the notion that the LGI1-ADAM22 complex functions as the trans-synaptic machinery for precise synaptic transmission and its disruption causes epilepsy.

Disclosures: Y. Miyazaki: None. A. Yamagata: None. N. yokoi: None. Y. Fukata: None. S. Fukai: None. M. Fukata: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

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Program #/Poster #: 039.24/F10

Topic: B.10. Epilepsy

Title: Downregulation of molecules mediating inhibitory neurotransmission in a NHE6 knock-out mouse model of Christianson syndrome

Authors: *A. Y. GAO, L.-C. MASSON, T. F. JAMES, R. A. MCKINNEY
Pharmacol. & Therapeut., McGill Univ., Montreal, QC, Canada

Abstract: Christianson Syndrome (CS) is an X-linked neurodevelopmental disorder characterized by intellectual disability, epilepsy, ataxia, and autistic behaviour. CS is the result of mutations in the *Slc9a6* gene encoding organellar Na⁺/H⁺ exchanger isoform 6 (NHE6), a regulator of endosomal pH that is thus essential for endosomal trafficking. In neurons, trafficking mechanisms are vital for the proper transport of molecules mediating neurotransmission. We have previously reported that NHE6 plays a role in learning and memory, as NHE6 is upregulated in the hippocampus during neurodevelopment and is recruited to excitatory synapses following activity. However, very little is currently known of how the loss of NHE6 function leads to the development of epilepsy in CS. Such work is crucial, as these patients routinely experience a large number and variety (*i.e.* tonic, tonic-clonic, myoclonic) of seizures. To this end, we investigated potential mechanisms that may lead to the attenuation of inhibitory regulation in *Slc9a6*^{-/-} mice. In their hippocampi, we found a significant downregulation of glutamate decarboxylase 67 (GAD67), an enzyme crucial for the production of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), compared to wild-type (WT) mice. Next, we employed markers for disparate inhibitory interneuron populations and found significant losses of parvalbumin- and somatostatin-positive cells. We then probed for molecules involved in inhibitory postsynaptic function and discovered a significant loss of the ionotropic GABA_A receptor α 1 subunit, yet no significant alterations in the α 2 subunit or the inhibitory scaffolding protein gephyrin, compared to WT hippocampi. Further experiments assessing K⁺/Cl⁻ cotransporter 2 (KCC2), which is critical for Cl⁻ homeostasis and thus proper GABAergic signaling in mature neurons, also showed reduced expression in adult KO animals relative to WT. Together, these data from *Slc9a6*^{-/-} mice suggest a dysregulation of both pre- and postsynaptic inhibitory neurotransmission within their hippocampal circuitry. Interestingly, whole cell patch clamp recordings from hippocampal area cornu ammonis 1 (CA1) pyramidal neurons revealed a significant increase in action potential firing in response to current injections of increasing magnitude in acute slices prepared from KO mice compared to WT, suggesting that *Slc9a6*^{-/-} CA1 pyramidal cells demonstrate intrinsic hyperexcitability as well. Overall, the present study is an initial step towards elucidating how epilepsy may develop in CS patients and will ideally set the groundwork for further understanding of this phenotype. Funding: CIHR, NSERC, HBHL.

Disclosures: A.Y. Gao: None. L. Masson: None. T.F. James: None. R.A. McKinney: None.

Poster

039. Epilepsy

Location: SDCC Halls B-H

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Program #/Poster #: 039.25/F11

Topic: B.10. Epilepsy

Support: Duke University
Edward Mallinckrodt Jr. Foundation

Title: Repeated stimulation of excitatory neurons in piriform cortex decreases feedback inhibition, leads to a loss of GABAergic neurons and reduces parvalbumin expression

Authors: *B. H. RYU, P. LEE, K. M. FRANKS
Neurobio., Duke Univ., Durham, NC

Abstract: Seizures are implicated as causal factors in the development of epilepsy and the progression of seizure severity. Yet, the cellular and molecular mechanisms that underlie this phenomenon remain elusive. The kindling model of epilepsy has been used to study the progressive increase in seizure severity. Traditionally, kindling involves repeated electrical initiation of focal seizures that become progressively more severe. Some studies have identified a kindling-induced loss of inhibitory interneurons and decreased synaptic inhibition. However, it could not be determined whether this loss was due to a gradual decrease in inhibition as a result of pathological levels of circuit activity during seizures or, instead, was simply an artifact of direct, strong electrical stimulation. To resolve this issue, we selectively expressed channelrhodopsin-2 (ChR2) in a subset of piriform cortex (PCx) principal cells, a highly recurrent and epileptogenic limbic circuit. We then directly co-activated these ChR2-positive ensembles several times per day with brief light trains delivered by an implanted optic fiber above the injection site (20Hz trains for 5s 6x/day). Optical stimulation initially had minimal effect. However, within 4 days of “optokindling”, brief stimulation reliably triggered a cascade of seizure activity that culminated in massive running-jumping seizures. To reveal the neural circuit processes underlying this phenomenon, we isolated acute brain slices from optokindled and sham-control mice and used whole-cell patch-clamp recordings to examine changes in synaptic connectivity. Optokindling disrupted the balance of recurrent excitation-feedback inhibition in ipsilateral PCx. This disruption was due to a marked, pathway-specific decrease in feedback inhibition. Consistent with this result, we observed a loss of GABAergic inhibitory interneurons in PCx of kindled mice. To provide molecular insight into this loss, we stained for parvalbumin (PV), as fast-spiking PV+ interneurons are partly responsible for feedback inhibition in PCx. We not only observed pronounced decreases in both the number of PV+ cells, but also in the levels of PV expression in these cells. Future studies are required to understand if and how PV expression levels alter the excitation-inhibition balance in this circuit. Our results

show that high levels of activity in excitatory neurons embedded within a recurrent cortical circuit induce a progressive and pathological downregulation of inhibition.

Disclosures: B.H. Ryu: None. P. Lee: None. K.M. Franks: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.01/F12

Topic: B.10. Epilepsy

Support: 323530-158125

Title: Large-scale 4-Hz oscillations control the expression of neocortical fast-ripples in hippocampal sclerosis

Authors: *L. SHEYBANI¹, P. VAN MIERLO², G. BIROT³, K. SCHALLER⁴, M. SEECK⁵, C. MICHEL³, C. QUAIRIAUX³

¹Fundamental Neurosci., Functional Brain Mapping Laboratory, Fac. of Me, Geneve, Switzerland; ²Med. Image and Signal Processing Group, Ghent Univ., Ghent, Belgium;

³Functional Brain Mapping Laboratory, Dept. of Fundamental Neuroscience, Univ. of Geneva, Geneva, Switzerland; ⁴Neurosurg. Division, Dept. of Clin. Neuroscience, Fac. of Medicine, Geneva Univ. Hosp., Geneva, Switzerland; ⁵Neurol. Division, Dept. of Clin. Neuroscience, Fac. of Medicine, Geneva Univ. Hosp., Geneva, Switzerland

Abstract: A conceptual shift in our understanding of focal epilepsy has led to the recognition that epileptic networks (EN), and not solely the localized brain region named “epileptic focus” (EF), are major pathogenic factors of the disease. However, how large-scale EN recruit distant pathological nodes, and whether this promotes the emergence of pathological activities remote from the focus remain largely unknown. Here, we show that neocortical fast-ripples (FRs) are generated in hippocampal sclerosis and are triggered by large-scale synchronizing 4-Hz waves that start in both hippocampi and then spread to frontal regions. These slow oscillations constrain bursts of paroxysmic 20-30 Hz activity to which neocortical FRs are time-locked. We further show that slow oscillations favor the generation of FRs through a modulation of neuronal firing, as we observed a strong phase-coupling of action potentials over the 4-Hz phase during these events. These low- and high-frequency coupling mechanisms demonstrate an intriguing parallel with cross-frequency coupling observed in certain physiological brain functions. Thus, similar mechanisms might underlie normal and pathological brain functions that rely on large-scale networks.

Disclosures: L. Sheybani: None. P. Van Mierlo: None. G. Birot: None. K. Schaller: None. M. Seeck: None. C. Michel: None. C. Quairiaux: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.02/F13

Topic: B.10. Epilepsy

Support: NIH

Title: Dissecting ictogenesis in a model of post-traumatic epilepsy

Authors: *L. A. LAU, K. LILLIS, K. STALEY
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Abstract: Acquired epilepsies are characterized by spontaneous, recurrent seizures that emerge following injury. Brain injuries account for 20-60% of all epilepsy and one third of patients with post-traumatic epilepsy are refractory to current treatment options. In order to guide the development of new treatment options, we need to know more about the process of seizure initiation, or “ictogenesis”, in chronically epileptic networks. In this study, we investigated the patterns of preictal activity in the hippocampal organotypic slice culture model of post-traumatic epilepsy. These slice cultures become spontaneously epileptic following the widespread axotomy that occurs during slicing. Slice cultures were prepared on P6-8, and were immediately placed on membrane inserts in a glass-bottomed 6-well plate. Organotypic slice cultures were then transferred to the Incuscope: a CO₂ incubator customized to include optics for inverted fluorescence microscopy, a motorized stage for positioning the samples, and a computer-controlled multi-channel perfusion pump, which allowed for the longitudinal study of network activity, with single cell resolution. Calcium dynamics were serially imaged in both principal cells and interneurons using the red calcium sensitive transgenic fluorophore jRGECO, over the course of several weeks. Ictal activity began to emerge over the first week post-injury and by DIV10, we could reliably detect hundreds of interictal spikes and ~10 seizures per hour. We found that each slice culture developed a stereotyped region which drove both spikes and seizures. However, there was considerable variability in the activation pattern of individual neurons within this region. Future studies will aim to parse the contribution of principal cell and interneurons in the preictal buildup to seizure initiation.

Disclosures: L.A. Lau: None. K. Lillis: None. K. Staley: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.03/F14

Topic: B.10. Epilepsy

Title: Local network synchronization in the rat dorsal and ventral hippocampus throughout development

Authors: S. MYSIEWICZ¹, *K. A. DOUGHERTY²

¹Neurosci. Program, ²Dept. of Biol., Rhodes Col., Memphis, TN

Abstract: Medial temporal lobe epilepsy (mTLE) is a prevalent form of focal epilepsy defined by spontaneous recurring seizures generated within the medial temporal lobe, with seizure foci that originate within the hippocampus being especially common. Interestingly, the probability that the local hippocampal network will synchronize and precipitate a seizure varies with location along longitudinal hippocampal axis, such that the anterior hippocampus (rather than the posterior hippocampus) is most often associated with seizure generation and hippocampal sclerosis. Moreover, the seizures associated with mTLE tend to begin during adolescence, and continue into adulthood. Given the age, and location dependence of seizure generation in the hippocampus, we sought to explore the mechanisms of local network synchronization across the longitudinal hippocampal axis throughout development using Sprague-Dawley rats ranging from two weeks to six months old. Here, network synchronization was accomplished by applying 0 mM Mg²⁺ artificial cerebrospinal fluid to acute hippocampal slices at near physiological temperature (31-33C), while network activity was monitored using an extracellular electrode placed in the cell body layer. Interestingly, the dorsal hippocampus (DHC; the rodent homolog of the human posterior hippocampus) transitioned from hyperexcitable to hypoexcitable (determined by steady-state event frequency) throughout development, whereas the activity within the ventral hippocampus (VHC; the rodent homolog of the human anterior hippocampus) remained stable throughout this developmental timeframe. This result suggests significant remodeling of the local circuits within the DHC throughout development, which presumably protect this region from inappropriate network synchronization, and, by extension, and could shed light onto the mechanisms of the seizure generation in adolescents with mTLE.

Disclosures: S. Mysiewicz: None. K.A. Dougherty: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.04/F15

Topic: B.10. Epilepsy

Title: High density multi electrode array: A new tool to monitor seizure-like activity evoked by different convulsant drugs

Authors: *M. SESSOLO, A. UGOLINI¹, A. MACCIONE², M. GANDOLFO², M. CORSI¹, C. VIRGINIO¹

¹Drug Design & Discovery, Aptuit, an Evotec Co., Verona, Italy; ²Brain AG, Waedenswille, Switzerland

Abstract: Temporal lobe epilepsy is the most common form of epilepsy. Symptoms consist of partial convulsive seizures spreading from hippocampal and para- hippocampal regions. Since one third of patients are unresponsive to antiepileptic drugs, development of new therapeutic molecules is crucial. Although no experimental model reproduces all features of TLE, *in vitro* models represent a useful tool to investigate the effect of new molecules in acute epileptic-like activity. In order to test different convulsant drugs, a fundamental step is to monitor in time and in space the abnormal activity preceding generation and the mechanisms involved in the propagation of epileptic-like activity. To that end, we monitor epileptic-like activity in adult mouse hippocampal slices with high-density multi electrode array (HD-MEA) composed by 4096 electrodes in a field of 8 mm². In spite of single electrode recordings, MEA is characterized by an unprecedented spatio-temporal resolution with high sensitivity and specificity. Indeed, signals can be investigated in terms of local field potentials (LFP) as well as spiking activity in order to monitor and quantify the effects of convulsants in different cortical-hippocampal areas involved in the epileptic-like activity.

In particular, we challenge slices with two kainate receptors agonists characterized by different selectivity, *i.e.* kainic acid (1 μ M) and the high-selective agonist (RS)-2-Amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl) propanoic acid (ATPA). In 6 slices from 3 mice, application of 10 μ M ATPA induced seizure-like activity in hippocampal-cortical circuitry lasting from several seconds to minutes. In detail, we observed strong activation in terms of LFP and spiking activity of hippocampal CA1 pyramidal neurons and cortical deep layers. Notably, consecutive ATPA applications induced comparable seizure-like activity that can be abolished when slices are perfused with normal bath solution. Furthermore, we compare the effect of these convulsants with 4-aminopyridine (100 μ M) model of epileptic-like activity in order to assess different mechanisms of generation and propagation of epileptic-like activity.

Disclosures: A. Ugolini: None. A. Maccione: None. M. Gandolfo: None. M. Corsi: None. C. Virginio: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Program #/Poster #: 040.05/F16

Topic: B.10. Epilepsy

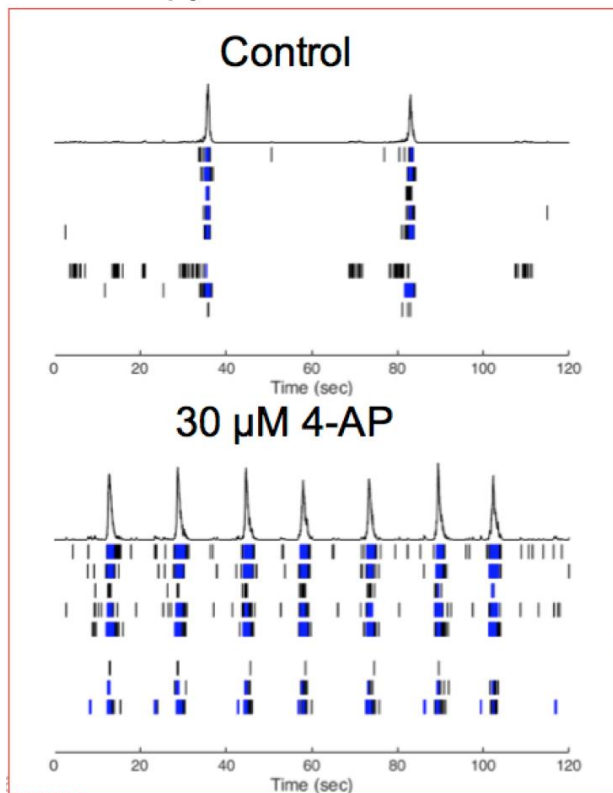
Title: Hesi neutox pilot study: Seizure liability assessment using hipsc-derived cns-like neural co-cultures

Authors: C. FLEMING¹, D. HESS², M. KENNEDY¹, T. PALM³, *G. C. LUERMAN¹

¹Ncardia Inc, Plymouth Meeting, PA; ²Ncardia AG, Cologne, Germany; ³Ncarida AG, Cologne, Germany

Abstract: Innovative, higher throughput, and predictive models are always required to address the evolving needs of preclinical R&D and safety assessment. Human neurons derived from induced pluripotent stem cells present a predictive, flexible and potent tool due to their unlimited availability, physiological relevance and lack of interspecies translatability issues. Human iPSC-derived neurons express physiologically-relevant levels of neurotransmitters. This can help to accelerate the assessment of clinically relevant issues such as psychological disorders, drug-induced seizure liability, peripheral neuropathy, and other CNS-related issues. HESI has established the "NeuTox" consortium to validate new pre-clinical, in vitro models to address the seizurogenic potentials of new chemical entities, Within NeuTox, it was agreed to use MEA (extracellular field potential) recordings to evaluate the predictive value of either animal-derived primary or hiPSC-derived neural models using 11 reference drugs with various known mechanisms of action and clinical seizurogenic risk. As a member of NeuTox, we tested all 11 drugs in 4 concentrations and 3 replicates using 48 well MEA recordings and hiPSC-derived CNS.4U neural co-cultures. The data shown here summarize these results, revealing that the seizurogenic risk of 10 of 11 compounds were correctly identified. This implies that hiPSC-derived CNS.4U neurons are an excellent model to assess seizurogenic risk of new compounds in vitro.

4-Aminopyridine



Disclosures: **C. Fleming:** A. Employment/Salary (full or part-time);; Ncardia. **D. Hess:** A. Employment/Salary (full or part-time);; Ncardia. **M. Kennedy:** A. Employment/Salary (full or part-time);; Ncardia. **T. Palm:** A. Employment/Salary (full or part-time);; Ncardia. **G.C. Luerman:** A. Employment/Salary (full or part-time);; Ncardia.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.06/F17

Topic: B.10. Epilepsy

Title: Neuron-glia interactions underlie state transitions to generalized seizures

Authors: ***E. YAKSI**¹, **C. DIAZ VERDUGO**², **S. MYREN-SVELSTAD**¹, **C. DENEUBOURG**¹, **R. PELGRIMS**¹, **N. JURISCH-YAKSI**¹

¹Norwegian Univ. of Sci. and Technol., Trondheim, Norway; ²Kavli Inst. for Systems Neurosci., Trondheim, Norway

Abstract: The transitions from normal brain activity to a generalized seizure are dramatic, and may lead to brain damage or even death. However, it is unclear how local oscillatory neuronal activity leads to sudden bursts of generalized neuronal activity invading the entire brain, often crossing boundaries between brain regions. Neuron-glia interactions are proposed to be important for seizure generation, especially due to the direct role of astrocytes for the regulation of neuronal excitability and synaptic transmission. It is, however, less clear how such interactions between neurons and glia underlie state transitions of neuronal networks leading to generalized seizures. To address this, we performed in depth analysis of the activity of thousands of individual neurons and glia across the zebrafish brain. Our findings suggest that while the number of active neurons increases preceding generalized seizures, the activity levels of active neurons remain unaffected. Moreover, our data suggest that the synchrony of the brain network increases within and across brain regions, during the period preceding the generalized seizures. We found that the transition from a local oscillatory state to a generalized seizure is abrupt and cannot be explained by the gradual changes of the network connectivity and synchrony. Instead, we observed that the explosion of network activity and the initiation of generalized seizures corresponds to a period where glial activity reaches its peak and neuron-glia networks are highly synchronized. Finally, we showed that glial activity strongly modulates the neuronal activity. Hence, we propose that changing homeostatic interactions across and neuron-glia is a potential mechanism for the manifestation of generalized seizures.

Disclosures: E. Yaksi: None. C. Diaz Verdugo: None. S. Myren-Svelstad: None. C. Deneubourg: None. R. Pelgrims: None. N. Jurisch-Yaksi: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Program #/Poster #: 040.07/F18

Topic: B.10. Epilepsy

Support: Epilepsy Research UK
Medical Research Council (UK)

Title: Divergent paths to seizure: Evidence from *in vitro* models of epilepsy

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Abstract: Epileptiform activity appears to evolve in similar ways in models of epilepsy as well as in the human condition. The first discharges often appear as interictal-like events that progress

into seizures over time. These patterns can be reproduced over a short timescale using in vitro models of epilepsy and have been widely used to gain insight into the human condition. Two of the most commonly used in vitro epilepsy models are the 0 Mg²⁺ model and the 4-aminopyridine (4AP) model. We will demonstrate that while both these models display seizure-like events, the route by which the epileptiform activity progresses is fundamentally different. Using paired patch-clamp recordings and Ca²⁺ network imaging, we will show that early activity in the 0 Mg²⁺ model involves strong glutamatergic drive and pyramidal cell activity that is continuously opposed by the interneuron populations. When this inhibition fails, seizure-like activity results. However, in the 4AP model, early activity emerges mostly from the interneuron populations, with limited pyramidal cell activity. We propose that this leads to chronic chloride loading of the pyramidal cells, thus increasing K₀ via the potassium chloride cotransporter 2. Indeed, we will demonstrate how altered K₀ influences seizure development between these two models. Furthermore, we will show that there are fundamental differences in the evolution of seizure-like activity between different brain regions in these two models, most strikingly between the neocortex and the hippocampus. These differences in the two models have important implications for the pharmacosensitivity of the relevant brain networks. Importantly, we will demonstrate that a thorough understanding of how these models generate seizure activity serves to enhance their utility for investigating mechanisms underlying epileptic seizures in humans.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.08/F19

Topic: B.10. Epilepsy

Support: Wellcome Trust
EPSRC

Title: Controlling abnormal network dynamics with optogenetics targeting excitatory cells

Authors: ***B. ZAAIMI**, A. HAZRA, Y. WANG, S. BAKER, M. KAISER, A. TREVELYAN, M. CUNNINGHAM, F. LEBEAU, A. JACKSON
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Abstract: We are investigating feedback control of oscillatory network dynamics by using local field potential (LFP) recordings to drive closed-loop optogenetic stimulation (CLOS). The aim is to develop reliable methods to modulate normal and abnormal activity patterns via active cancellation or enhancement of oscillations, for scientific and therapeutic purposes. Here we

report results from in silico computational modelling, in vitro brain slice experiments with EMX-ChR2 mice as well as in vivo demonstrations under terminal anesthesia in EMX-ChR2 mice as well as non-human primates that had previously been injected with AAV8-CAG-Chronos-GFP. In these experiments, the LFP was first band-passed and phase-shifted using a finite impulse response filter. The output of the filter was half-wave rectified and modulated continuously the intensity of excitatory optogenetic stimulation. We examined the LFP power spectrum under CLOS with different filter frequencies (5Hz, 10Hz, 20Hz and 40Hz) and phase-shifts (0, 45, ..., 315 deg). In addition, we investigated the effect of CLOS on the duration of seizure-like events elicited by 4-Aminopyridine. CLOS produced a phase-shift-dependent modulation of LFP power for filter frequencies between 5 to 20 Hz but not at 40 Hz, with some phase-shifts eliciting a sustained oscillation at the filter frequency. At other phase-shifts, power was reduced relative to control conditions with no stimulation. Following bath application of 4-AP in vitro, or intracortical injection in vivo, bursts of oscillatory seizure-like events were elicited. As before, CLOS was capable of modulating the LFP power associated with these events. Moreover, phase-shifts that increased/decreased oscillatory power could also increase/decrease the duration of seizure-like events relative to control conditions with no stimulation. These results could be explained by our in silico simulations using a Wilson-Cowan model in which seizures resulted from a bistable limit cycle in phase space. Excitatory stimulation delivered to the excitatory population at the appropriate phase-shift could destabilise this limit cycle and increase the probability of the network returning to the stable region of phase space. We conclude that CLOS is an effective means of modulating oscillatory activity at a range of frequencies. Depending on the phase-shift used, CLOS can either suppress or enhance oscillations in a predictable and controllable manner. Moreover, appropriate CLOS can reduce abnormal activity during seizure-like episodes, with potential application in the treatment of focal epilepsy.

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Poster

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Program #/Poster #: 040.09/F20

Topic: B.10. Epilepsy

Title: Dysregulation and restoration of homeostatic network plasticity in fragile X syndrome mice

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Abstract: Chronic activity perturbations in neurons induce homeostatic plasticity, through modulation of synaptic strength or intrinsic properties, to maintain the correct physiological range of excitability. However, whether such a process occurs at a population level and what molecular mechanisms are involved remain unclear. In the current study, we utilized a multielectrode array (MEA) recording system to evaluate homeostatic neural network activity of cultured primary mouse cortical neurons. We demonstrated that chronically elevated neuronal activity through inhibition of GABA(A) receptors elicits synchronization of neural network activity and homeostatic reduction of the amplitude of spontaneous neural network spikes. We subsequently showed that this phenomenon is mediated by the ubiquitination of tumor suppressor p53 that is triggered by murine double minute-2 (Mdm2). Using a mouse model of fragile X syndrome in which fragile X mental retardation protein (FMRP) is absent (*Fmr1* knockout), we found that Mdm2-p53 signaling, network synchronization, and the reduction of network spike amplitude upon chronic activity stimulation were all impaired. Pharmacologically inhibiting p53 with Pifithrin- α or genetically employing *p53* heterozygous mice to enforce inactivation of p53 in *Fmr1* knockout cultures restores the synchronization of neural network activity after chronic activity stimulation and partially corrects the homeostatic reduction of neural network spike amplitude. Together, our findings reveal the roles of FMRP and Mdm2-p53 signaling in the homeostatic regulation of neural network activity and provide insights into the deficits of excitability homeostasis when FMRP is compromised, such as occurs with fragile X syndrome.

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Poster

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Topic: B.10. Epilepsy

Support: Brain and Behavior Research Foundation
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Title: Epilepsy-associated mutations of Nedd4-2 disrupt AMPA receptor-dependent neuronal network activity

Authors: *J. ZHU¹, K. LEE², K. A. JEWETT², H.-Y. MAN³, H. CHUNG², N.-P. TSAI²
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Urbana-Champaign, Urbana, IL; ³Boston Univ., Boston, MA

Abstract: The neural precursor cell expressed developmentally down-regulated gene 4-2, *Nedd4-2*, is an epilepsy-associated gene with at least three missense mutations identified in epileptic patients. *Nedd4-2* encodes a ubiquitin E3 ligase that has high affinity toward binding and ubiquitinating membrane proteins. However, it is currently unknown how *Nedd4-2* mediates neuronal circuit activity and how its dysfunction leads to seizures or epilepsies.

In this study, we provide evidence to show that *Nedd4-2* mediates neuronal activity and seizure susceptibility through ubiquitination of GluA1 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, (AMPA). Using a mouse model, termed *Nedd4-2^{andi}*, in which one of the major forms of *Nedd4-2* in the brain is selectively deficient, we found that the spontaneous neuronal activity in *Nedd4-2^{andi}* cortical neuron cultures was basally elevated, less responsive to AMPAR activation, and much more sensitive to AMPAR blockade, compared to wild-type cultures. When performing kainic acid-induced seizures *in vivo*, we showed that elevated seizure susceptibility in *Nedd4-2^{andi}* mice was normalized when GluA1 is genetically reduced. Furthermore, all three epilepsy-associated missense mutations of *Nedd4-2* disrupted the ubiquitination of GluA1 and failed to reduce spontaneous neuronal activity *in vitro*. Taken together, our data suggest that impaired GluA1 ubiquitination contributes to *Nedd4-2*-dependent neuronal hyperactivity and seizures.

To our knowledge, our findings provide the first mechanism underlying *Nedd4-2*-associated circuit hyperactivity and seizures and open up a new avenue for the development of therapeutic strategies to potentially treat epileptic patients who carry *Nedd4-2* mutations.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Program #/Poster #: 040.11/F22

Topic: B.10. Epilepsy

Support: NIH U01 NS090414

Title: Amygdala lesions prevent seizure-induced respiratory arrest and death in two mouse models of SUDEP

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Abstract: Sudden Unexpected Death in Epilepsy (SUDEP) is the most common cause of death in refractory epilepsy patients. Results from human studies and animal models suggest that respiratory arrest is commonly the initiating event leading to death. In a refractory epilepsy patient, we demonstrated a correlation between seizure spread into the amygdala and apnea. Apnea can be reproduced by electrical stimulation of the amygdala. These results suggest that the amygdala may act as a critical node in the pathway for seizures to spread from the cortex to the brainstem, leading to respiratory arrest (S-IRA) and death. The aim of the current work was to determine if the amygdala is a necessary structure in the pathway leading to S-IRA and death in two mouse models of SUDEP. Experiments were performed on *Scn1a*^{R1407X/+} mice, a model of Dravet syndrome (DS), that have spontaneous and heat-induced seizures, and on DBA/1 mice that have audiogenic seizures. Both mouse strains have a high incidence of fatal respiratory arrest after seizures. Under isoflurane anesthesia, bilateral focal electrolytic lesions targeted the amygdala. Data were compared to mice that had lesions outside of the amygdala (controls), or received sham lesions. EEG and EKG electrodes were implanted for tethered recordings. Temperature telemetry probes were implanted in the flank. Mice were allowed to recover for 5 days. To induce seizures, DS mice were exposed to a heat lamp to increase body temperature from 37°C to 42.5°C at a rate of ½°C/min. DBA/1 mice were exposed to an alarm bell for up to 60 sec. EEG, EKG, body temperature, plethysmography and video were continuously recorded during seizure induction. The locations of lesions were verified by Nissl staining or immunohistochemistry for NeuN. Electrolytic lesions of the amygdala prevented fatal S-IRA in 55.5% of DBA/1 (n=9) and 90.9% of DS (n=11) mice despite Racine scale 5 seizures. In contrast, only 8% of DBA/1 (n=14 control and n=10 sham) and 30% of DS mice (n=4 control and n=6 sham) without amygdala lesions survived full seizures. These differences were statistically significant (DBA/1 & DS p<.01). Histology revealed that amygdala lesions were protective even when they were localized correctly on only one side (DBA/1 n=4/5, DS n=9/10). Current work is focused on replicating these experiments with kainic acid lesions. These results indicate that postictal apnea and death in DS and DBA/1 mice requires bilateral intact amygdalae. We hypothesize that seizures cause apnea when they propagate from the hippocampus/forebrain through the amygdala and invade the brainstem respiratory network, and this pathway through the amygdala is required for fatal respiratory arrest.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Program #/Poster #: 040.12/F23

Topic: B.10. Epilepsy

Title: *In vitro* neuronal network models of SCN2A epileptic encephalopathy

Authors: *L. JIA^{1,2}, S. PACHERNEGG¹, M. LI¹, N. JANCOVSKI¹, B. ROLLO¹, T. KARLE¹, S. MALJEVIC¹, C. REID^{1,2}, S. PETROU^{1,2}

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Abstract: Epileptic encephalopathies are a group of devastating childhood disorders presenting with refractory seizures, severe developmental delay, intellectual disability and movement disorders. *SCN2A*, which encodes the brain sodium channel Na_v1.2, has emerged as one of the most prominent epileptic encephalopathy genes. Patients with *SCN2A* epilepsy variants can be divided into two groups based on age of onset of seizures. In the early onset group seizures start within the first three months of life, while in the second group, the onset is after three months of age. Sodium channel blockers are often effective in the former, but rarely in the latter group, suggesting different pathomechanisms. We have generated two knock-in mouse lines carrying mutations corresponding to human R1882Q and R853Q variants, which are the most common variants found in the early and the late onset groups, respectively. *In vitro* signatures of neuronal network behaviour were assessed using multielectrode arrays (MEA) analysis of the primary cortical cultures obtained from P0-P2 wildtype and mutant mice. After 2-4 weeks the R1882Q culture neuronal networks showed increased activity while the R853Q networks showed decreased activity relative to wild type. These results support the idea that early onset disease is due to molecular and cellular gain-of-function. Despite seizures emerging in the late onset group the primary molecular and cellular effect of the mutation is loss of function suggesting secondary epileptogenesis as a consequence of this reduced function.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.13/F24

Topic: B.10. Epilepsy

Title: Pharmacological blockade of KCC2 in the subiculum triggers synchronized inter-ictal like bursts

Authors: *M. P. FISKE¹, G. MACCAFERRI²

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Abstract: A prominent theory regarding the development of epileptic hyper-synchronization in human and animal models of temporal lobe epilepsy proposes a key role for the specific down-regulation of the KCC2 transporter in subicular pyramidal cells¹. As KCC2 is essential to maintain the low intracellular chloride concentrations required for hyperpolarizing GABAergic signaling, loss of KCC2 expression would impair GABAergic inhibition and trigger a series of events leading to the emergence of subicular-initiated interictal activity. Although this prediction was supported by computational modeling², direct experimental evidence based on the pharmacological block of KCC2 has not yielded definitive results. Here, we have utilized simultaneous triple cell-attached and whole-cell recording to evaluate the role of KCC2 on network activity and synchronization in the isolated subiculum. Our preliminary data show that the application of a highly selective KCC2 antagonist (VU0463271, 10 μ m) on isolated mini-slices of the mouse subiculum generate synchronous interictal-like bursting that depends on depolarizing GABAergic signaling, but are not, apparently, sufficient to trigger ictal-interictal transitions. These events are pharmacologically similar to the inter-ictal events seen in patients, as they can be abolished by application of AMPA or GABA receptor antagonists. Additionally, our preliminary data suggests that epileptiform synchronization in the subicular mini-slices requires excitatory input from parvalbumin+ cells. Brief (1-2 ms) photoactivation of PV+ interneurons expressing channelrhodopsin in slices exposed to the KCC2 antagonist triggered interictal-like spikes that were electrophysiologically similar to spontaneously occurring events. In contrast, prolonged (15 sec) light stimulation of PV+ cells suppressed KCC2 antagonist induced bursting. Our results support the hypothesis that the down-regulation of KCC2 is sufficient to elicit epileptiform activity in otherwise healthy subicular networks. 1. Miles R, Blaesse P, Huberfeld G, Wittner L, Kaila, K (2012) Chloride homeostasis and GABA signaling in temporal lobe epilepsy. In: Noebels JL, Avoli M, Rogawski MA, et al., editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US). 2. Buchin A, Chizhov A, Huberfeld G, Miles R, Gutkin BS

(2016) Reduced Efficacy of the KCC2 Cotransporter Promotes Epileptic Oscillations in a Subiculum Network Model. J Neurosci 36, 11619- 11633.

Disclosures: M.P. Fiske: None. G. Maccaferri: None.

Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Burroughs Wellcome Fund Career Award for Medical Scientists

Title: Imaging single neuron activity during the transition to a seizure in a mouse model of Dravet syndrome links micro- and macro-scale dynamics

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Abstract: How complex network-level phenomena such as seizures emerge from the activity of individual, defined subsets of interconnected neurons remains a fundamental, yet unsolved, question in epilepsy research. Extensive prior investigations into the mechanisms of epilepsy and the initiation and propagation of seizures have focused either at the level of individual neurons, or at the scale of the electroencephalogram (EEG); the ability to link single neuron dynamics and large-scale EEG across these scales remains limited. Here, we use two-photon calcium imaging to study the activity profiles of individual neurons during the transition to a seizure in an experimental mouse model of Dravet syndrome (DS). DS is a severe childhood-onset epilepsy defined by treatment-resistant and temperature-sensitive seizures along with developmental delay/intellectual disability autism spectrum disorder, and increased rate of seizure-related death, due to loss of function heterozygous mutation of *SCN1A* encoding the type 1 voltage gated sodium channel alpha subunit Nav1.1. Prior studies in mouse models (*Scn1a*^{+/-} mice) suggest that DS pathogenesis involves the dysfunction of cerebral cortical GABAergic inhibitory interneurons (INs), particularly parvalbumin-positive INs (PV-INs). We record the simultaneous activity of hundreds of individual neurons in layer 2/3 of the sensorimotor neocortex in awake head-fixed *Scn1a*^{+/-} mice that are free to run on a spherical treadmill and are exposed to passive

elevation of core body temperature. During the transition to seizure, there is an overall increase in the firing rate of pyramidal neurons; dimensionality reduction and clustering techniques reveal that this increase is driven by a progressive recruitment of initially quiet cells into an active state. Overall, our results reveal that progressive changes in the activity patterns of functionally defined subgroups of neurons play important roles in driving seizure activity.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 040.15/F26

Topic: B.10. Epilepsy

Support: NIH R01NS099586

Title: Glucose modulation of thalamocortical neuron excitability

Authors: *K. A. SALVATI¹, D. R. WYSKIEL², M. P. BEENHAKKER³
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Abstract: The link between diet and epilepsy remains unresolved, particularly for epilepsies characterized by spike-and-wave discharges (SWD). Herein, we provide several lines of evidence demonstrating that thalamocortical circuits implicated in SWD generation are glucose-sensitive.

Using video-EEG, we first demonstrate that low glucose intensifies SWDs in two rodent models [DBA/2J mouse (D) and WAG/Rij rat (W)]. In both models, SWD count increases following a 16 hour fast ($p < 0.05$, $n = 12D$; 13W animals). Also, seizure exacerbation generally correlates with decreased blood glucose levels ($p < 0.05$; $p < 0.001$, $n = 12D$; 13W animals). To disambiguate the effects of hypoglycemia and hyperketonemia on SWDs, we monitored seizures following insulin injection, a manipulation that results only in the former. Insulin injection increased SWD occurrence in DBA/2J mice ($p < 0.05$, $n = 10$) and trended so in WAG/Rij rats ($p = 0.17$, $n = 11$). These data indicate that low glucose, not elevated ketone bodies, modulates SWD occurrence. Current- and voltage-clamp recordings performed in acutely prepared brain slices demonstrate that brief exposure to low glucose alters the intrinsic excitability of thalamocortical (TC) neurons. We observed both glucose-excited (GE) and glucose-inhibited (GI) TC neurons, a dichotomy similar to that reported with comparable assays performed in the hypothalamus. Patch-clamp data identified TC neurons that exhibited a significant hyperpolarization ($p < 0.05$, $n = 8D$ cells) or depolarization ($p < 0.5$ $n = 4D$; 9W cells) in low glucose. Collectively, our electrophysiological data suggest the presence of GE/GI TC neurons. We further validated the

presence of GE and GI TC neurons using calcium imaging (GCaMP) approaches. Neuronal glucokinase (GCK) expression plays an important role in conferring glucose-sensitivity to cells. GCK acts synergistically with ATP-sensitive potassium channels (KATP) to depolarize GE neurons. We performed immunohistochemistry and observed co-expression of KATP channels and GCK. Moreover, patch-clamp recordings from TC neurons demonstrate functional KATP-channel expression. Application of diazoxide, a KATP channel agonist, generated a dose-dependent outward current in TC neurons. Moreover, the effect was occluded by the KATP channel antagonist, glibenclamide. These data support the presence of GE, TC neurons. In sum, we demonstrate that glucose modulates thalamocortical excitability and may lead to an increase in SWDs. Our data lends support to the hypothesis that certain extrinsic factors, like diet, influence the occurrence of epileptic activity in the brain.

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Poster

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Program #/Poster #: 040.16/G1

Topic: B.10. Epilepsy

Support: NIH R01NS069861 & R01NS097750

Title: Disruption in theta/gamma oscillatory dynamics *in vivo* in a rodent model of experimental epilepsy

Authors: *D. SUBRAMANIAN^{1,2}, J. PALMIERI², V. SANTHAKUMAR^{1,2}

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Abstract: Disruption of coherent network activity is believed to underlie cognitive deficits in epilepsy. Interneuron networks are critical for shaping network activity and achieve this through synaptic connections to principal neurons and mutual connectivity between homotypic and heterotypic interneuron subtypes. In earlier *ex vivo* studies, we examined cell type specific interneuronal connectivity in the dentate gyrus of rats following pilocarpine induced status epilepticus (SE) and identified preserved homotypic connectivity between fast-spiking basket cells (FS-BC). However, synaptic release from heterotypic, cannabinoid sensitive interneurons to FS-BCs was reduced due to an aberrant increase in presynaptic GABA-B activation (Yu et al 2016). Simulation studies incorporating these changes in biologically-based dentate network models predicted strong perturbations in theta /gamma oscillatory dynamics resulting in the breakdown of theta/gamma coupling. This study was conducted to test the model prediction and examine changes in oscillatory dynamics after pilocarpine induced SE *in vivo*. Dentate

oscillations were recorded from the granule cell layer of urethane anesthetized male Wistar rats 4 weeks after pilocarpine induced SE. Age matched saline treated rats served as controls. Spectral analysis of data was performed using LabChart and custom written codes in Matlab. Our preliminary analysis revealed a shift in the peak theta (4-12 Hz) and gamma (30-90 Hz) frequencies in post SE rats compared to saline controls (n=4 rats each). Analysis of total power in theta and gamma bands revealed a decrease in theta and an increase in gamma power in post SE rats. More importantly, a reduction in theta/gamma ratio was observed in post SE rats, consistent with our model predictions. Ongoing studies are testing the role of pre-synaptic GABA-B receptors in altered theta/gamma dynamics following pilocarpine induced SE. Our results *in vivo* confirm our predictions based on *ex vivo* and *in silico* studies. Further validation of the mechanistic findings *in vivo* will open a new avenue to test the effectiveness of GABA-B antagonists in rescuing behavioral and cognitive deficits in epilepsy.

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Poster

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Topic: B.10. Epilepsy

Support: University of Virginia Medical Scientist Training Program
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Title: A heterogeneous thalamic network model that recapitulates oscillations modulated by GABA transporter blockade

Authors: *A. C. LU¹, C. K. LEE³, B. TRUONG², J. R. HUGUENARD³, M. P. BEENHAKKER²

¹Med. Scientist Training Program, ²Pharmacol., Univ. of Virginia, Charlottesville, VA; ³Dept Neurol & Neurolog. Sci., Stanford Univ. Sch. Med., Palo Alto, CA

Abstract: Absence seizures are thought to result from 3~5 Hz generalized thalamocortical oscillations. Understanding how such oscillations persist could lead to novel treatments for the most common form of pediatric epilepsy. Previous work has shown that electrically-induced oscillations in acute thalamic slices were prolonged upon pharmacological blockade of GABA transporters GAT1 or GAT3 individually, but were surprisingly suppressed upon dual blockade of GAT1 and GAT3. Using pharmacological manipulations, distinct temporal profiles of inhibitory post-synaptic currents (IPSCs) from GABA_B receptors of thalamocortical (TC) relay neurons could be recorded for each of 4 pharmacological conditions: (1) control, (2) GAT1 blockade, (3) GAT3 blockade, (4) dual blockade. We propose that the differential effects of GAT

blockade on thalamic oscillations could be accounted for by the differential activation of GABA_B receptors in TC neurons. To this end, we developed a biophysical thalamic network model that can recapitulate differences in oscillations when GABA_B activation profiles were varied. We first established 3-compartment single TC neuron models that could recapitulate differences in GABA_B IPSC responses. Using dynamic clamp, voltage responses to each of the 4 GABA_B IPSC conductance profiles, at 3 different levels of maximal amplitude, as well as voltage responses to a current impulse, was recorded for 36 TC neurons. In general, TC neurons had an increase in low-threshold spike (LTS) probability with GAT1 or GAT3 blockade but a significant decrease with dual blockade. However, there was also high IPSC response heterogeneity among the 36 neurons. By fitting simulated current impulse responses and simulated IPSC responses for each individual cell, we sought to infer geometric and conductance parameters for all 36 neurons. Finally, we incorporated the heterogeneous model TC neurons into an established thalamic network model. A homogeneous network model was sufficient to recapitulate the exacerbation of oscillations with GAT1 or GAT3 blockade and the abolishment of oscillations with dual blockade. Nevertheless, network heterogeneity seemed to be necessary for modelling seizure termination. In summary, we have developed a biophysically-based computational model that recapitulates most effects of GABA transporter antagonists on thalamic oscillations. These results suggest that modulation of GABA transporters is a potential novel treatment for absence epilepsy.

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Poster

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Topic: B.10. Epilepsy

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Title: Assess circuit excitability using acute and chronic silicon probe recordings in ankyrin-G knockout mice

Authors: *D. G. SUCHANEK, A. J. WILLIAMS, Q.-Q. SUN
Zoology and Physiology- Univ. of Wyoming, Laramie, WY

Abstract: Genome-wide association studies have pin-pointed to the scaffolding protein ankyrin-G, encoded by the gene *ANK3*, as a possible risk locus for bipolar disorder. Homozygous Ankyrin-G knockout mice (*Ank3-Ib^{KO/KO}*) have been instrumental in deciphering the role ankyrin-G plays in

both the central and peripheral nervous systems. It forms protein complexes between integral membrane proteins, such as voltage-gated sodium and potassium channels, and the underlying cytoskeleton, enabling the clustering of these components at the axon initial segment (AIS) and nodes of Ranvier. Previous work has focused on the molecular aspects of this transgenic mutant with some behavioral testing examining specific drug treatments. Only recently have *in vitro* slice recordings and EEG studies been performed to begin to understand the physiological defects brought on by an absence of ankyrin-G. It was found that parvalbumin (PV+) expressing interneurons showed a reduced intrinsic excitability. Fast-spiking PV+ interneurons are recruited by the canonical sensory circuits are the key player of the feedforward inhibition. To our knowledge the resulting aberrant activity has not been investigated thoroughly in this *Ank3-Ib^{KO/KO}* mouse mutant. In the present study, linear silicon probes were used to investigate both spontaneous and stimulus evoked activity in the barrel cortex of acutely anesthetized homozygous *Ank3-Ib^{KO/KO}* mice and compared these results to their wild-type (WT) counterparts. Long-term population recordings using chronic probes further expanded our knowledge about this mutant. Extracellular recorded activity of all three recording paradigms (acute w/o sensory stimulation and chronic) was examined at various frequency bands, including LFPs, MUAs, and high frequency oscillations (>80 Hz). Current source density analyses provided laminar profiles within the cortical barrel field and extending subcortically into the hippocampus and thalamus. Furthermore, anesthesia-induced burst suppression events were used to examine the hyperexcitability caused by the impaired PV+-expressing interneurons. Examining population activity using multi-electrode silicon probes in these homozygous *Ank3-Ib^{KO/KO}* mice will provide us with a more thorough understanding of the wiring within the cortical microcircuitry. While the essential roles of ankyrin-G at the cellular level have been investigated in numerous publications, focus needs to be put on how this protein affects neurons at the population level. This will lead to more insights into the association of *ANK3* to the debilitating disease of BD.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

Location: SDCC Halls B-H

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Program #/Poster #: 040.19/G4

Topic: B.10. Epilepsy

Support: NIH Grant NS033310
NIH Grant NS065877

Title: Association between epileptiform activity and reduced fMRI connectivity in the default mode network in the kainic acid rat model of epilepsy

Authors: L. HE^{1,2}, L. LI¹, C. B. KHALIL¹, H. J. YEH¹, N. HARRIS^{3,4}, J. STERN¹, J. ENGEL, Jr.^{1,3,5}, *A. BRAGIN^{1,3}

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Abstract: The current study aims to investigate the resting-state functional brain connectivity (rsFC) changes during an early period of epileptogenesis. Sprague-Dawley rats (n=19) were injected with kainic acid in the left CA3 area of the hippocampus to induce status epilepticus (SE). One week before and 2 weeks after SE, 10 minutes of rsFC data were acquired using a single-shot, gradient-echo, echo-planar, functional magnet resonance imaging 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). After the second fMRI session at 2 weeks post-SE, depth electrodes were implanted in the bilateral Prelimbic cortex, Anterior Cingular cortex, Motor cortex and Dorsal/Ventral Hippocampus. Wide-band electrical activity was recorded continuously for 4 weeks. Rats that exhibited epileptiform interictal spikes and/or seizure activity were selected for a further, combinatorial analysis of fMRI and EEG data (n=10). After preprocessing, image data were co-registered to an anatomical template and analyzed by independent component analysis (ICA) to identify the default mode network (DMN), and to guide the selection of additional regions-of-interest (ROIs) for seed-based assessment of rsFC. ICA analysis revealed the existence of a DMN at baseline and at 2-week after SE. Six bilateral ROIs were selected for rsFC analysis within the DMN. Significant decrease of rsFC was observed in many ROI pairs, while the most profound changes were observed between lesioned hippocampus and ipsilateral prefrontal cortex. The presence of pathological EEG patterns was associated with reduced bilateral rsFC of BOLD signals during epileptogenesis. Our study suggests a potential link between the changes of rsFC within the DMN, and the occurrence of pathological EEG patterns during the early period of epileptogenesis.

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Poster

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Topic: B.10. Epilepsy

Support: NIH Grant NS033310
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Title: Functional and structural properties of epileptogenic networks in the kainic acid rat model

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Abstract: We posit that understanding the multi-scale, connectomic reorganization of the epileptic brain will boost the development of new biomarkers to help prevent and cure epilepsy. The current study utilized a rat model of chronic status epileptics (SE) induced by kainic acid (KA) injection into the left, CA3 hippocampal region. We combined deep brain electrophysiological recordings and ex-vivo DTI to assess both functional and structural abnormalities after SE. Three groups of animals were investigated that: (1) developed epilepsy after SE (E+, n=8), (2) did not develop epilepsy (E-, n=6), and (3) served as sham controls (n=6). Following KA injection, bipolar electrodes were positioned at 5 locations bilaterally in the brain (peri-limbic cortex, anterior cingulate, anterior thalamus, CA1, and Dentate Gyrus) and were used to record EEG for 2 months. Data were quantified for local field potentials occurring during slow wave sleep, gamma events coupling (GEC), and pathological high-frequency oscillations (pHFO). Following EEG data acquisition, ex-vivo DTI data were acquired using a 7Tesla spectrometer. A structural connectome was constructed using a co-registered, parcellated atlas with 122 gray matter regions of interest using streamline counts. Graph theory analysis was used to for analytical inference of changes in network topography. We observed pHFOs in the majority of the brain areas recorded within E+ animals but no pHFOs were observed in E- and in sham control animals. We also found a decrease in EEG-analyzed functional connectivity, as indicated by suppression of GEC between ipsilateral CA1 and prefrontal cortex, and this was restricted to the E+ group of animals. The imaging data revealed significant decreases of FA values in internal capsule (p=.003), fimbria (p=.001), fornix (p=.018) and corpus callosum (p=.02) in E+ compared to E- and sham control. We observed modifications at the local network level that was indicated by an obvious reduction in the number of network hubs in ipsilateral prefrontal cortex, and a paradoxical increase in hub centrality in contralateral prefrontal cortex and bilateral hippocampal-thalamic regions in E+ animals. Combining imaging and EEG data, we observed a robust association between the occurrence of pHFO, reduction of GEC and change in hubness within the ipsilateral thalamic-hippocampal-prefrontal cortex network in E+ animals. The convergence of the data obtained through functional and structural network analysis to ultimately reveal an altered circuit suggests that combining imaging and EEG methods is a feasible approach for understanding brain reorganization that occurs during epileptogenesis.

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Poster

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Support: We wish to thank the Allen Institute for Brain Science founders, Paul G. Allen and Jody Allen, for their vision, encouragement and support.

This work is done in close collaboration with the Blue Brain project, EPFL, Switzerland.

Title: Human dentate gyrus granule cell morpho-electric properties are correlated with the severity of hippocampal sclerosis

Authors: *A. BUCHIN¹, R. DE FRATES¹, P. CHONG¹, M. RUSTY¹, K. DAI¹, U. RUTISHAUSER^{2,3}, R. GWINN⁴, S. SORENSEN¹, J. TING¹, C. A. ANASTASSIOU^{1,5}
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Abstract: Epilepsy is the fourth most common neurological disorder, and is responsible for a greater total global burden of disease than any neurological conditions except for stroke and migraine (Chin et al., 2014; Beghi et al., 2005; Rothstein et al., 2005). Despite considerable advances in the treatment and diagnosis of seizure disorders, about 40% of patients remain pharmaco-resistant (Fisher et al 2015). Seizures are often accompanied by hippocampal sclerosis, characterized by Wyler Grade (WG), ranging from 0 to 5, from less to more severe case (e.g. Cendes et al. 1995). To determine the mechanisms underlying epileptogenesis in the human brain we analyzed in vitro data to study the excitability of hippocampal neurons in tissue obtained from brain surgery for treatment of focal, pharmacoresistant epilepsy. We systematically analyzed the morphological and electrophysiological properties of human hippocampal dentate gyrus granule cells with different degrees of hippocampal sclerosis (WG1 vs. WG4). We find that spiking properties such as time to first spike, first inter-spike interval (ISI) and mean ISI are correlated with WG, while passive properties such as input resistance and the resting potential are not. The majority of morphological properties of single-neurons do not correlate with the degree of hippocampal sclerosis, further pointing to an excitability difference as the most prominent single-neuron biomarker. Furthermore, we found differences in numbers and density of spines associated with the WG. To test the implications of the observed differences under realistic scenarios, we developed biophysically detailed computational models of single neurons with active dendrites capable to reproduce the key electrophysiological features of human hippocampal granule cells as a function of WG. Using these models we explored

relevant pathophysiological scenarios associated with hippocampal sclerosis and its implications for the mechanisms underlying increased excitability associated with epilepsy.

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Topic: B.10. Epilepsy

Support: EU, Human Brain Project, H2020-720270
EU FLAG-ERA, SlowDyn project
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BFU2017-85048-R

Title: Can ephaptic coupling participate in intercolumnar synchronization in neocortex?

Authors: ***A. DESTEXHE**¹, **B. REBOLLO**², **A. NAVARRO-GUZMAN**², **M. V. SANCHEZ-VIVES**^{2,3}, **B. TELENCZUK**¹

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Abstract: Neurons interacting via synaptic mechanisms in a conductive medium generate extracellular electric fields (EFs) that in turn affect the membrane potential. Thus, a feedback loop emerges between synaptic activity and EFs in neuronal networks. Externally applied EFs have been shown to modulate synaptic activity (Frohlich and McCormick *Neuron*, 67: 129, 2010; Anastassiou et al. *Nature Neuroscience*, 14: 217, 2011; D'Andola et al., *bioRxiv*, 246819, 2018). However, the complete feedback loop that might contribute to the synchronization of neurons still remains unclear. Here, we combine in vitro experiments and computational models to evaluate if endogenously generated oscillations can synchronize via electric-field effects. On the experimental side, we used an in vitro preparation of ferret cerebral cortex that generates slow synchronized oscillations (Sanchez-Vives and McCormick, *Nature Neuroscience*, 3: 1027, 2000). We performed a complete vertical cut of the slice, perpendicular to the cortical surface. This resulted in two synaptically independent networks, each of which had its own oscillatory pattern. The vertical cut allowed isolating synaptic transmission from the EF propagation. We then characterized how the EF induced by slow wave oscillations on one side propagated across the cut to the adjacent network and its impact on the oscillatory synchronization. On the modeling side, we designed a biophysical model of slow oscillations and explored the EF effects generated by the emergent activity. We used a mean-field representation of a column of

excitatory-inhibitory networks. Each pyramidal neuron's dipole produced an endogenous electric field that propagated laterally to the neighboring neurons. We calculated the EF generated by a population of pyramidal cells, as well as the effect of the EF on the membrane participating in the synchrony. When connecting two cortical columns via EFs, mimicking the cut slice experiments, we found a weak synchronizing effect between the two columns (0.01 mV depolarization in all cells, simultaneously). However, when several columns were placed in a 2D arrangement representing the cortical sheet, the synchronizing effect was much stronger (1-2% simultaneous increase of firing rate). This increase was enough to trigger a consecutive UP state in a bistable mean-field model, thus contributing to the synchronization of the columns. We conclude that EF-effects play a significant role in the large-scale synchronization of cortical columns.

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Poster

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Program #/Poster #: 040.23/G8

Topic: B.10. Epilepsy

Support: We thank the Allen Institute founders, Paul G. Allen and Jody Allen for their support

Title: Multi-modal investigation of subthreshold and spiking entrainment to externally imposed electric fields in mouse V1

Authors: *F. BAFTIZADEH¹, S. LEE¹, S. GRATIY¹, T. CUNNINGTON², K. DAI¹, S. OLSEN¹, C. ANASTASSIOU^{1,3}

¹Allen Inst. For Brain Sci., Seattle, WA; ²Univ. of Washington, Seattle, WA; ³Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The application of electric stimulation to the brain has been widely used to probe the physiological processing of brain activity as well as for therapeutic interventions in neurological disorders such as epilepsy, Parkinson's disease and essential tremor. In addition, there has been increased interest and progress incorporating brain stimulation to drive brain-machine interfaces for sensory and motor devices. However, the use of neural prosthetic to address cognitive physiology and pathology remains incomplete. There is still a lack of understanding about where, when, and how to apply an extracellular field to brain circuits *in vivo*, leading to conflicting outcomes regarding the efficacy of electric brain stimulation to modulate higher-level brain processing. At the same time, cognitive impairment remains one of the least tractable and most debilitating aspects in a wide variety of neurological disorders such as autism, epilepsy,

depression and schizophrenia. The Allen Institute for Brain Science has developed a large-scale, unified approach for the robust and reproducible deconstruction of cortical circuitry to understand how the interplay of components gives rise to high-level processing [1]. We leverage this infrastructure to build a similar approach to dissect and understand the elements of brain stimulation parameters and its effects. Our primary goal is to offer mechanistic understanding at multiple spatial levels during stimulation so as to enhance the selectivity, specificity and efficacy of electric stimulation protocols. Specifically, we have utilized a combination of biophysically detailed simulation workflow (allowing the exploration and permutation of key parameters in electrical stimulation entrainment) in combination with novel, multi-patch brain slice experiments to understand electric field effects at the single-neuron level. We demonstrate the effect of different extracellular stimulus parameters such as amplitude, frequency and phase on sub-threshold and spiking responses of single neurons in mouse V1 and explore various types of field entrainment.[1] Koch C and Reid R. C., Observation of the mind, Nature (2012)

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Poster

040. Epilepsy: Networks, Dynamics, and Computation

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Topic: B.10. Epilepsy

Support: NIH Grant R01-NS050434

Title: Differential optogenetic modulation of parvalbumin and somatostatin inhibitory interneuron activity downregulates seizure activity in the mouse temporal neocortex

Authors: ***F. PUCCI**¹, **S. J. CRUIKSHANK**², **B. W. CONNORS**²
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Abstract: We investigated the role of parvalbumin (PV)- and somatostatin (SOM)-expressing inhibitory interneurons in seizure genesis using optogenetic and electrophysiological techniques. Channelrhodopsin-2 (ChR2) or archaerhodopsin (ArchT) was expressed in PV or SOM interneurons using Cre recombinase mouse lines in order to allow for bidirectional modulation of these neuronal populations. Acute coronal brain slices (250 μ m) were prepared from mice (P21-28) and maintained in artificial cerebrospinal fluid. Paired whole-cell recordings of layer 5 pyramidal cells and either PV or SOM interneurons were performed in the temporal neocortex. The K channel blocker 4-aminopyridine (25 μ M) was applied in order to lower the seizure threshold. An electrographic ictal event could be evoked reproducibly by electrically stimulating the tissue (85% of attempts). Then, peri-stimulation photoactivation of ChR2 or ArchT was used

to either excite or inhibit PV and SOM cells.

ChR2-mediated excitation of PV interneurons at the time of eliciting an evoked seizure induced inhibitory postsynaptic currents (IPSCs) in cortical pyramidal cells. But this intervention did not result in any reduction in the probability of evoking seizure-like events (89% of trials).

Activating ChR2 in SOM interneurons, however, substantially reduced the probability of generating an evoked seizure (26%) relative to control conditions. There was no difference between the PV-ChR2 and SOM-ChR2 cohorts with respect to mean IPSC magnitude measured in cortical pyramidal cells ($p=0.22$), suggesting that the mechanism of SOM-mediated reduction in seizure activity is likely not simply due to direct inhibition of pyramidal cells alone.

Paradoxically, optical inhibition of PV interneurons with ArchT resulted in a significant decrease in the probability of generating an evoked seizure (33%).

We therefore present here specific instances in which both driving and inhibiting the activity of GABAergic neurons can lessen ictogenesis in an in vitro model of neocortical seizure activity.

Moreover, these phenomena are specific to different interneuron subpopulations. The mechanisms by which the activity of PV and SOM interneurons modulate the probability of seizure generation is as yet unknown. Taken together, these data suggest that subtypes of cortical interneurons play different but critical roles in the generation of epileptiform activity, and that optogenetic modulation of these neuronal populations warrants further investigation as a potential antiepileptic intervention.

Disclosures: F. Pucci: None. S.J. Cruikshank: None. B.W. Connors: None.

Poster

041. Epilepsy: Seizure Mechanisms

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Topic: B.10. Epilepsy

Support: DOD Award #W81XWH-16-1-0660

Title: The HDAC inhibitor sodium butyrate reduces neuropathology and behavior dysfunction after traumatic brain injury in mice

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¹Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX; ²Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Traumatic brain injury (TBI) is a major cause of mortality and morbidity worldwide, particularly in military personnel, with large direct and indirect costs to society. Recent evidence suggests that epigenetic HDAC inhibition may reduce the development of epilepsy and improve functional outcomes. Epigenetics, which refers to a set of functional changes in gene expression

without altering the DNA, is emerging as a critical driver in many brain diseases. However, the potential of treatments based on epigenetic pathways have not been widely tested in PTE. In this study, we tested the efficacy of the class I/II HDAC inhibitor, sodium butyrate, on PTE. TBI was induced in mice by a CCI paradigm and a recording electrode was placed in the contralateral hippocampus. Behavioral and motor analyses were assessed over a 4-month period and tests consisted of beam-walk, neuroscore, plus-maze, open-field, Morris water-maze and NORT. Brains were fixed for histochemistry and analyzed for principal neurons (NeuN+), interneurons (PV+), astrocytosis (GFAP+), microgliocytosis (IBA1+), and neurogenesis (DCX+). There was extensive neurodegeneration of principal and inhibitory interneurons at 4 months after TBI. Massive reactive gliosis and astrocyte activation persisted from week 1 till 4 months, indicating persistent neuroinflammation after TBI. Untreated TBI mice showed extensive deficits in motor, sensory and cognitive function. Our results show that the cognitive and sensory-motor outcomes were significantly improved with butyrate treatment compared to control cohort. Butyrate therapy significantly reduced brain lesion size, neurodegeneration, neuroinflammation, and mossy fiber sprouting. These histological results were correlated to improved behavioral outcomes in butyrate group. Our results demonstrate the potential of HDAC inhibition as a potential neuroprotection therapy for TBI, especially to attenuate chronic comorbidities.

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Poster

041. Epilepsy: Seizure Mechanisms

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Topic: B.10. Epilepsy

Support: Swedish Research Counsel

Graduate Mixed Mobility Scholarships for Studies Abroad Program 2017 (as visiting researcher) The National Council of Science and Technology, Mexico 470980/291062

Title: Enantiomeric N-substituted phthalimides with excitatory amino acids protect zebrafish larvae against PTZ-induced seizures

Authors: *C. CAMPOS RODRIGUEZ^{1,2}, E. RAMIREZ-SAN JUAN³, R. OLSSON²

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Abstract: Epilepsy is a neurological disease that affects around of 1 % of the world population. One third of the patients with active epilepsy are refractory to the pharmacological therapies, so it is necessary to find new pharmacological therapies to treat the disease.

Thalidomide is an active molecule, that was discovered as an anti-seizure drug. It is constituted by a phthalimide and glutarimide moieties. Phthalimide group has been studied as pharmacophore in some *N*-phthaloyl amino acids due to the important biological activities in the organism. For the *in vivo* screening of drugs, a variety of animal species has been employed. Zebrafish (ZF) has been an excellent model for the screening of new molecules for epilepsy. Phthaloyl-aspartate (RTA, STA) and phthaloyl-glutamate (RTG, STG) are the drugs in study for this work. They are chiral molecules, due to the fusion of the phthaloyl ring with the excitatory amino acids, which gives the chance to study the couple of enantiomeric compounds in the PTZ model in ZF. Acute PTZ exposure in ZF larvae evokes seizure-like activity that could be quantified, usually between 5-7 days post-fertilization (dpf).

To evaluate functionality of the blood brain barrier (BBB), the convulsive behavior was evaluated in 7 and 10 dpf ZF larvae with a 20 mM PTZ exposure. The larvae were placed in well-plates and one hour prior to the PTZ exposure, the treatments were added: control (DMSO 2%), control-PTZ 20 mM, sodium valproate (SVP) 3 mM, and two concentrations of *R*-phthaloyl glutamate (RTG; 100 and 316 μ M). Immediately after the 60 min, PTZ solution was added per well with exemption of the control group. The larvae's behavior was analyzed for 45 after the exposure. With the results of the aforementioned study, the anticonvulsant effect of the glutamate and aspartate phthalimides enantiomers were tested following the same method at 237.1 and 316 μ M concentration in 10 dpf ZF.

The findings of the study suggest that the function of the BBB at 7 dpf is enough to protect ZF against PTZ 20 mM with RTG 316 μ M and SVP 3 mM. The same effect of the two drugs was appreciated at 10 dpf. However, the locomotor activity of the ZF is significantly increased at 10 dpf compared with the 7 dpf age. Considering that the BBB of the ZF is completely formed at 10 dpf, the four phthalimides had been tested at this age. The four molecules have the properties to antagonize the PTZ 20 mM seizure-like behavior at 316 μ M, furthermore, RTG has the same effect at 237.1 μ M.

Phthalimides *N*-substituted with excitatory amino acids suggest being potent anticonvulsants acting in the GABAergic system. Moreover, the enantiomer *R* of the phthaloyl-glutamate might be more selective than the *S*; it has activity since 237.1 μ M.

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Poster

041. Epilepsy: Seizure Mechanisms

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Topic: B.10. Epilepsy

Support: AES Grant 411837 (ALB)
R56NS096234 (ALB)

Title: Complement C3 contributes to seizure-induced behavioral deficits in mice

Authors: *N. D. SCHATZ, A. L. BREWSTER

Psychological Sci., Purdue Univ., West Lafayette, IN

Abstract: Epilepsy is comorbid with cognitive and psychiatric dysfunctions. This pathophysiology, associated with hippocampal synaptodendritic structural and functional changes, is exacerbated by prolonged seizures (status epilepticus; SE). We found a correlation between hippocampal dendritic loss and microgliosis after SE, along with hyperactivation of the classical complement pathway (C1q-C3). These paralleled increased seizure frequency and memory deficits in a rat model of SE and acquired epilepsy. C1q leads to C3 cleavage into biologically active fragments C3a and C3b. Evidence suggests that C1q and C3b contribute to synaptic stripping by microglia in the developing brain and neurodegenerative disorders. Thus, we hypothesized that SE-induced C3 activation may alter hippocampal function thereby promoting memory deficits. To test the hypothesis, different groups of wild type (WT) or C3 deficient (C3KO) mice were injected with pilocarpine (350mg/kg) to induce SE or saline (controls): WT-C, WT-SE, C3KO-C, and C3KO-SE. Hippocampi were collected at 1hr of SE to measure markers of neuronal activity (cFos and p-S6) using immunoblots (n=3). Two weeks after SE, a different group was subjected to open field (OF) and novel object recognition (NOR) (n=7-8) to evaluate locomotion and recognition memory, respectively. In OF, we measured distance travelled, speed, freezing, and time in the inner portion of the arena. For NOR, mice explored 2 similar objects for 10min. After 5 days they explored a familiar and a novel object and exploration time measured. Pilocarpine induced level 5 seizures (SE) according to the Racine scale in both WT and C3KO mice. Hippocampal protein levels of cFos and p-S6 increased after SE in WT and C3KO mice. OF: WT-SE mice showed increased distance traveled ($p<.01$) and speed ($p<.01$), along with decreased freezing ($p<.01$) compared to WT-C mice, while WT-C, C3KO-C, and C3KO-SE performed similarly in all OF measures ($p>.05$). NOR: In trial 1, exploration time for both objects was similar in all groups ($p>.05$). In trial 2, WT-C and C3KO-C mice spent more time exploring the novel object than the familiar one ($p<.05$) while WT-SE mice explored both objects equally ($p>.05$). Interestingly, C3KO-SE mice spent more time with the novel object similar to controls ($p>.05$), suggesting that the deficit in object recognition memory induced by SE was attenuated in C3KO mice. We were able to induce SE at similar levels in WT and C3KO mice. Thus, the OF/NOR data suggest that SE-induced C3 hyperactivation may contribute to altered locomotion and anxiety behaviors as well as memory deficits. Ongoing studies are focusing on the role of C3 in the SE-induced hippocampal neuropathology.

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Poster

041. Epilepsy: Seizure Mechanisms

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Topic: B.10. Epilepsy

Support: NIH Grant NS078644

Title: Development of a laser scalpel neurosurgical approach to treat focal neocortical epilepsy

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Abstract: Epilepsy affects about 5% of dogs and 3% of humans. In cortical focal epilepsy, seizures initiate at one location in the brain and propagate to other regions. About 30% of such cases are not responsive to anticonvulsants, leaving resective neurosurgery, which may impact brain function, as the only current alternative. One potentially less invasive approach would be to sever lateral neural connections seizures propagate along rather than resecting the seizure-prone tissue, but this would require the capability to make precise cuts inside the cortex without causing extensive collateral damage (for example, to the blood vessels on the brain surface). Tightly-focused femtosecond infrared laser pulses can act as a laser scalpel with the capacity to ablate tissue in a micrometer-sized focal region located up to ~2 mm into the brain while leaving surrounding structures intact. Previous rodent studies from our lab showed that severing lateral connections within the supragranular layers of the neocortex with a laser cut that surrounded an acutely induced seizure focus resulted in a 63% reduction in the number of seizures that propagated beyond the cut and abolished seizure propagation in some animals. These cuts largely preserved the health and function of the neurons located inside the cut, including their ability to respond to a peripheral stimulus. In ongoing work, we aim to test the longer-term efficacy of this approach. Injection of nanoliter quantities iron chloride into the neocortex is used to induce chronic focal epilepsy and electrodes are implanted to measure local field potential at different distances from the resulting seizure initiation site. With this model we observe between 5 and 15 focally-initiated seizures per hour beginning a few weeks after injection, while we see no seizures in controls. We will next determine whether femtosecond laser cuts surrounding the injection site reduces the propagation of seizures to distant electrodes. The animals with epilepsy and cuts will be compared to animals without epilepsy and cuts, animals with epilepsy and no cuts, and animals with just electrode implantation. We anticipate seizure propagation will be impaired by cuts severing lateral connections, while neural function should be relatively intact

due to the micrometer size nature of the cuts and the preservation of both the health of most neurons and their vertical connectivity within the cortical column.

Disclosures: **S. Lieberman:** None. **D.A. Rivera:** None. **R. Radwanski:** None. **M. Zhao:** None. **T.H. Schwartz:** None. **C.B. Schaffer:** None. **N. Nishimura:** None.

Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 041.05/H2

Topic: B.10. Epilepsy

Support: CURE Grant # 7153

Title: Immunization with mycobacterium vaccae prevents asd-like behavioral outcomes but not epileptogenesis in the stress-terbutaline model of epilepsy

Authors: ***Z. Z. SMITH**¹, R. A. KUBIAK¹, T. CRIST¹, C. A. LOWRY², D. S. BARTH¹
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Abstract: The neurological basis for Autism Spectrum Disorders and epileptogenesis remain largely unknown, but a significant portion of children diagnosed with ASD also develop chronic recurrent spontaneous seizures, suggesting that there could be a potential mechanistic link between the two developmental disorders. Recently, maternal stress has been shown to enhance the behavioral deficits in a rat model of autism and is necessary for the development of spontaneous seizures. While maternal stress has also been shown to be a significant risk factor for the development of social deficits in children, research on the mechanisms and potential interventions is lacking. Emerging evidence suggests a role for the gut-brain axis in neurodevelopmental disorders, putative CNS inflammation, and overactive response to psychosocial stressors, which could be a potential treatment target for ASD. Specifically, pathological outcomes of stress can be prevented by injections of a heat-killed preparation of *Mycobacterium vaccae* NCTC 11659, which has previously been shown to reduce stress-induced colitis and stress-associated behavioral impairments. Here we attempt to modulate the effects of maternal stress on the development of spontaneous seizures and behavioral deficits in the stress-terbutaline model of autism and epilepsy. Immunization of dams with *M. vaccae* (0.1 mg, s.c.; embryonic days 3, 10, and 17) followed by immunization of male offspring on postnatal days 7, 13, and 20, prevented the development of ASD-like behavioral deficits in the stress terbutaline model in rats, but had no effect on the development of spontaneous seizures or epileptiform activity. Behavioral severity, as indexed by a composite ASD score encompassing social communication and repetitive behavior, was not an adequate predictor of epilepsy risk. However, avoidance behavior, as measured by performance on the defensive burying task, was

significantly elevated in animals that later developed spontaneous seizures. These data suggest a role for the gut-brain axis in the negative effects of maternal stress and proposes a potential intervention that can reliably reduce behavioral deficits associated with ASD. However, these data also serve to disentangle the link between some autistic-like behaviors and the development of spontaneous seizures, suggesting that reductions in active coping (and not repetitive behaviors or social deficits) may be the most reliable behavioral predictor of seizure risk in this model.

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Poster

041. Epilepsy: Seizure Mechanisms

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Program #/Poster #: 041.06/H3

Topic: B.10. Epilepsy

Support: the National Natural Science Foundation of China 81671288

Title: *In vivo* direct reprogramming of reactive glial cells into neurons in a temporal lobe epilepsy model

Authors: *J. YU, J. ZHENG, T. LI, G. CHEN
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Abstract: Temporal lobe epilepsy is one common refractory disease accompanied with abundant cell death in hippocampus. Recently, our team discovered that a single neural transcription factor NeuroD1 can directly convert reactive glial cells into functional neurons (Guo et al., Cell Stem Cell, 2014). We used pilocarpine induced temporal lobe epilepsy rat model to test whether *in vivo* reprogramming could inhibit the development of epilepsy. One week after status epilepticus, we transfected hippocampal astrocytes with NeuroD1-expressed adeno-associated virus (AAV). One week after virus injection, we found prominent expression of neuronal marker protein NeuN in NeuroD1 expressing cells. Two months after infection, these cells presented the morphology of mature neurons, some of which were Gad67-positive interneurons. The distribution of reprogrammed neurons were similar as existed ones, as excitatory neurons resided on the band whilst inhibitor cells located outside. Compared with the control group, NeuroD1 transfection significantly increased the total number of hippocampal neurons and inhibitory interneurons, reduced the frequency of spontaneous recurrent seizures and ameliorated behavioral abnormalities. These data suggest that our *in vivo* reprogramming approach can effectively transform reactive glial cells into neurons to suppress seizures and to rescue behavioral deficits.

Disclosures: J. Yu: None. J. Zheng: None. T. Li: None. G. Chen: None.

Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 041.07/H4

Topic: B.10. Epilepsy

Support: NIH NINDS R21NS090250
NIH NINDS T32 NS095775

Title: G9a-mediated heterochromatin rearrangement in the dentate gyrus during epileptogenesis

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Abstract: There are currently no treatment options available to halt or prevent the development or epileptogenesis of temporal lobe epilepsy (TLE). The process of epileptogenesis involves large-scale changes in gene transcription contributing to the restructuring of synapses associated with increased hyperexcitability in the hippocampus. Recently, epigenetic mechanisms, including histone lysine methylation (HKM), have gained interest as regulatory mechanisms of gene expression dysregulation during epileptogenesis. HKM is an epigenetic modification that can result in either gene repression or activation depending on the histone lysine residue methylated and the degree of methylation (mono-, di- or tri-methylation). Alterations in synaptic function and abnormal neuronal gene regulation in the dentate gyrus (DG) region of the hippocampus contributes to TLE pathophysiology. Using the kainate (KA) unilateral intra-hippocampal experimental mouse model of TLE, we found that the heterochromatin mark histone H3 lysine 9 di-methylation (H3K9me2) is significantly decreased in the ipsilateral DG of KA infused mice as compared to saline infused controls. We found no significant changes in H3K9me2 levels in the DG of the contralateral hemisphere of KA infused animals. Next, we determined if manipulating the H3K9 histone methyltransferases G9a/GLP (EHMT2/1) in the DG alone was sufficient to effect seizure susceptibility. Using transgenic G9a floxed mice and intra-DG hSyn-Cre AAV viral infusions, we have confirmed knockdown of G9a and subsequent decreases in H3K9me2 levels in DG cell-type specific neurons. In addition, CRISPRa approaches were used to overexpress G9a, which resulted in significant increases in H3K9me2 levels. Chromatin immunoprecipitation analysis revealed changes in H3K9me2 levels at genes associated with TLE, like *Bdnf*, which is overexpressed during epileptogenesis. Video-EEG

monitoring suggest that demethylation of H3K9me2 increases spiking frequency and methylation of H3K9me2 dampens epileptiform activity in KA infused mice. Moreover, hippocampus-dependent memory testing suggest that H3K9me2 changes strongly correlate with memory deficits in KA-infused mice. Collectively, our data suggest that G9a mediates H3K9me2 levels in the epileptic hippocampus that are diminished in DG neurons and may lead to regulation of seizure susceptibility genes and epileptiform activity. By manipulating the heterochromatin mark, H3K9me2, we have identified a putative target for novel anti-epileptogenic therapeutics.

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Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 041.08/H5

Topic: B.10. Epilepsy

Support: NINDS grant #1U54NS079202

Title: Comparison of TETS and picrotoxinin pharmacokinetics in mice

Authors: *D. ZOLKOWSKA, F. KAMIENSKI, L. M. OLSEN, M. A. ROGAWSKI
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Abstract: Tetramethylenedisulfotetramine (TETS) is a highly lethal neurotoxic rodenticide that acts in a similar fashion to picrotoxinin as a noncompetitive GABA_A receptor antagonist. TETS is considered to be a high priority chemical threat agent but little is known about its pharmacokinetic properties, and it is unclear why TETS is so much more potent *in vivo* than picrotoxinin when the potencies of the two compounds for block of GABA_A receptors are similar. Here we determined the tissue distributions, including the brain penetration, of [¹⁴C]TETS and [³H]picrotoxinin in mice. Mice received a single intravenous (iv) infusion of aqueous solutions of the tracers, respectively, 0.045 μCi in 100 μl and 1.0 μCi in 200 μl. At various times after the injection (7 min - 7 days), animals were sacrificed and trunk blood along with selected organs were collected. Counts per minute values corrected for quenching per ml or g of tissue were calculated. A subset of mice received unlabeled TETS at a dose sufficient to induce clonic seizures (0.1 mg/kg, ip) and then immediately after the first seizure [¹⁴C]TETS was infused. [³H]Picrotoxinin counts in brain rose to a peak at 30 min (mean 0.19% of total radioactivity administered) and subsequently decreased during the 7 days after infusion (to 0.011%) while blood radioactivity was highest at the first (15 min) time point (1.07%) and then dropped to a fraction of this value (0.27%) at 7 days. A large fraction of the radioactivity was present in the liver and kidney at 15 min but the radioactivity dropped markedly between 15 and

30 min from 75.7% to 18.8% and from 5.9% to 2.8%, respectively. In the [¹⁴C]TETS experiments, the fraction of radioactivity in the brain was higher, beginning at 1.09% at 7 min and 0.93% at 30 min and then dropped to 0.59% at 60 min. A substantial fraction (0.23%) was found at the 7-day time point. Blood radioactivity dropped from 3.97% (7 min) and 3.30% (15 min) to 2.72% (30 min) and rose to 5.06% at 60 min while 2.43% was found at the 7-day time point. Both, liver and kidney radioactivity was lower than with [³H]picrotoxinin (from 2.60% at 15 min to 1.83% at 60 min and from 0.78% at 15 min to 0.57% at 60 min, respectively). We conclude that picrotoxinin is likely metabolized in the liver and excreted. In addition, it appears that picrotoxinin or its metabolites are also rapidly excreted in the kidney. By contrast, metabolism of TETS seems to be minimal. TETS-induced seizure activity did not increase brain penetration of [¹⁴C]TETS. The greater potency of TETS *in vivo* compared with picrotoxinin is likely due to its greater brain penetration. In addition, our results confirm that at least some portion of administered TETS remains in the body for prolonged periods.

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Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 041.09/H6

Topic: B.10. Epilepsy

Title: Investigation into serotonergic control of seizures via the 5-HT_{2C} receptor

Authors: *G. A. HIGGINS¹, L. B. SILENIEKS², N. RAMSEYER², E. VAN NIEKERK², C. TAYLOR³, S. KANTOR³, N. UPTON³

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³Transpharmation Ltd, London, United Kingdom

Abstract: Although the neurotransmitter serotonin is not traditionally associated with neuronal excitability and seizure control, two lines of evidence implicates serotonin signaling through the 5-HT_{2C} receptor in this process. Firstly the 5-HT releaser/reuptake inhibitor fenfluramine has been reported to provide positive benefit as an adjunctive treatment for Dravets syndrome, a severe childhood epilepsy with no effective therapy currently identified (Cuelemans et al (2012) *Epilepsia* 53: 1131-1139). Despite its generalized enhancement of 5-HT function, many effects of fenfluramine have been demonstrated to be dependent on 5-HT_{2C} receptor activation, suggesting that 5-HT_{2C} receptor activation may have an anticonvulsant property. Secondly, 5-HT_{2C} KO mice have been reported to be seizure prone (Tecott et al (1995) *Nature* 374: 542-546). Using a range of 5-HT_{2C} receptor agonists of varying selectivity (lorcaserin, CP-809101, Ro 60-0175, mCPP) and the selective 5-HT_{2C} antagonist SB-242084, the role of this receptor in the

regulation of seizures was investigated. In male CD-1 mice, pretreatment with the selective 5-HT_{2C} receptor agonists lorcaserin (1-30 mg/kg IP; N=6/group), CP-809101 (1-30 mg/kg IP; N=6/group) and Ro 60-0175 (3-30 mg/kg IP; N=6/group) did not prevent seizures elicited by MES (45mA), scPTZ (85 mg/kg) or 6Hz (44mA) stimulus, e.g. lorcaserin 0% inhibition (i.e. 0/6 protection) of seizures at 30 mg/kg against each seizure type. Conversely pretreatment with sodium valproate (300 mg/kg oral) was effective against each seizure type. In male Wistar rats implanted with a bipolar electrode into the basolateral amygdala, neither lorcaserin (1-10 mg/kg; N=6) nor mCPP (1-10 mg/kg; N=6) reliably affected EEG afterdischarge duration (ADD) or Racine kindling score in fully kindled (stage 5) rats following electrical stimulus delivery (e.g. Racine score: Veh 4.7±0.2; Lor 10 mg/kg 4.2±0.5). The effect of SB-242084 on EEG in fully kindled and “normal” rats was also investigated. Based on available data the present studies have failed to confirm a reliable effect of selective 5-HT_{2C} receptor agonists as effective anticonvulsants. However, the present studies have been confined to using supramaximal stimuli, and alternative seizure parameters may be required to detect an effect of this drug class on seizure control.

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Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 041.10/H7

Topic: B.10. Epilepsy

Support: DOD Grant PR161864
NIH Grant RO1 NS075366

Title: Application of a novel, probability-based algorithm to assess the development of epilepsy after traumatic brain injury (TBI)

Authors: J. A. PFAMMATTER¹, P. V. RODRIGUES², S. KONDURU², R. A. BERGSTROM³, *M. V. JONES¹, R. K. MAGANTI²

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Abstract: Traumatic brain injury (TBI) can lead to a wide range of sequelae including posttraumatic epilepsy (PTE). Epidemiological data suggest that as many as 20% of patients with TBI in the general population and up to 50% of patients injured in military service will develop epilepsy. There is evidence linking the severity of a TBI to the probability of developing PTE, however there still remains a large amount of uncertainty surrounding which patients will

ultimately develop PTE. Thus, identifying early markers that are predictive of PTE development is imperative. Here, we performed TBI (controlled cortical impact, CCI) on 8 CD-1 mice with electroencephalogram (EEG) recordings obtained 1 week, 2 months and 3 months following surgery. Visual inspection of EEG revealed that ~30% of TBI animals displayed seizures, often only at later time points, whereas almost all TBI animals had interictal spikes (IISs), spike clusters or trains at each time point. Therefore, nonconvulsive spikes may be a valuable predictor of later seizures but their quantitative scoring and characterization remains a major bottleneck to diagnosis. Here we apply a novel, probability-based algorithm (see Pfammatter et al. elsewhere at this meeting) to identify, categorize, and longitudinally track interictal activity from EEG. The algorithm first identifies events that ‘stand out’ of the background signal using a two-threshold method (events start if they cross 5 std above the signal mean and end when they cross 1 std below the mean). Then, identified events (across multiple animals and recording days) are concatenated, normalized, and projected into Principle Components (PC) space. The first three PCs are used to cluster events and calculate a probability of risk for epilepsy, based on the ratio of events within each cluster belonging to TBI versus sham-treated animals. We then correlated the events in each cluster with the incidence of electrographic seizures to establish which clusters hold events that are predictive of the development of PTE. Initial application of the algorithm in kainate-treated (KA) mice reveals successful prediction of risk for epilepsy. We find over 6x as many events above a threshold of 5 std in TBI animals as compared to KA animals. Three of the TBI animals developed convulsive seizures, one of which died as a result, and all three showed elevated predictive scores. Future studies will aim to determine which clusters (i.e., spike waveforms) are most predictive and whether this method can predict outcomes in response to early diagnosis and treatment during epileptogenesis.

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Poster

041. Epilepsy: Seizure Mechanisms

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Program #/Poster #: 041.11/H8

Topic: B.10. Epilepsy

Support: NIH Grant R01 NS097762

Title: Optogenetic modulation of striatal output pathways for seizure suppression in rodent epilepsy

Authors: *S. HYDER, P. A. FORCELLI

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Abstract: 65 million people worldwide have epilepsy. Of these, 60% have Temporal lobe epilepsy (TLE). Macrocircuit-level approaches for modulating neural network activity show promise for controlling seizures in an etiology-independent manner. To this end, silencing activity in the substantia nigra pars reticulata (SNpr) strongly protects against seizures in rodents as demonstrated by pharmacological inhibition or lesioning. While studies have delineated the roles of mid/hindbrain targets of SNpr in seizure control, the role of the upstream basal ganglia (BG) nuclei remains unclear. The striatum serves as the input nucleus of the BG and gives rise to two canonical parallel pathways that modulate SNpr. Activation of the striatonigral pathway silences SNpr, while silencing the striatopallidal pathway suppresses SNpr. However, neuronal subpopulations are not segregated within the striatum, so traditional approaches have not been able to isolate the pathways. With the advent of optogenetic and recombinant technologies, we can surmount this challenge by selectively expressing optogenetic actuators on genetically-defined neurons. Thus, we sought to examine each of these pathways using an optogenetic approach to elicit seizure control. We utilized the amygdala kindling model of TLE to evoke seizures and evaluated both electrographic and behavioral seizure manifestations. Adult male Long-Evans (L-E) rats from dopamine receptor D1 (D1)- and D2 (D2)-cre transgenic colonies obtained from NIDA were microinjected with cre-dependent optogenetic constructs bilaterally into striatum; fiber optics were placed bilaterally. Recording/stimulating depth electrode was placed into left basolateral amygdala (BLA). Animals were stimulated daily until they displayed 5 seizures with maximal behavioral manifestation, at which point they were tested. Animals were stimulated at a predetermined current threshold at baseline and with modulated light in randomized series on a within-subject basis. We compared this effect to pan-neuronal activation of the striatum (using an AAV-hSyn construct). Optogenetic activation of striatal D1-expressing neurons or optogenetic silencing of striatal D2-expressing neurons suppresses amygdala kindled seizures in rats. Rats display suppressed behavioral and electrographic seizure manifestations with optogenetic intervention.

Disclosures: S. Hyder: None. P.A. Forcelli: None.

Poster

041. Epilepsy: Seizure Mechanisms

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Program #/Poster #: 041.12/H9

Topic: B.10. Epilepsy

Support: R01NS097762

Title: Nigrotectal and nigropontine projections have divergent effects on seizure control

Authors: *E. WICKER¹, P. A. FORCELLI²

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Abstract: The potent anticonvulsant effect of pharmacological inhibition of the substantia nigra pars reticulara (SNpr), originally identified in the early 1980s by Gale and colleagues, has long been hypothesized to function by disinhibition of the deep and intermediate layers of the superior colliculus (SC). Consistent with this pharmacological or optogenetic activation of the SC is robustly anticonvulsant across models. However, the SNpr projects to other structures including the pedunculopontine nucleus (PPN). Pharmacological activation of the PPN has produced mixed effects across studies, with some reporting anticonvulsant effects. Selective targeting of nigral projections (i.e., SN-SC vs SN-PPN) was not attainable using pharmacological approaches. However, optogenetic methods now enable the direct targeting of these efferent pathways, and thus a direct test of these specific projections are now possible. Here, we compared the efficacy of optogenetic silencing of SN cell bodies, SN-SC projections, and SN-PPN projections across several models of experimentally-evoked seizures: systemic pentylenetetrazole (generalized seizures), focal microinjection of bicuculline into the “area tempestas” (focal limbic seizures), and systemic gamma butyrolactone (absence-like seizures). Rats were injected with AAV coding for either the inhibitory opsin, SwiChR or the inhibitory opsin ArchT in the SNpr and fiber optics were placed in the SNpr (to silence cell bodies). We compared these animals to those in which AAV-ArchT was injected into the SNpr and fiber optics were placed within the SC or PPN, to silence nigrotectal or nigrosegmental terminals, respectively. Focal inhibition of cell bodies within the SNpr was effective at suppressing seizures in each model examined. A similar profile of anticonvulsant action was seen after silencing nigrotectal (SN-SC) projections. However, silencing nigrosegmental produced a mixed effect. While inhibition of SN-PPN projections suppressed absence seizures, it worsened seizures evoked by PTZ. These data show that selective suppression of the nigral terminals in the SC, but not PPN is sufficient to account for the full spectrum of anticonvulsant effects achieved by inhibition of the SNpr. These data also indicate a functional divergence in this seizure control pathway, as silencing either nigrotectal or nigrosegmental projections disrupted absence seizures, but only silencing of nigrotectal projections disrupted PTZ-evoked seizures. The enhanced specificity provided by this approach may further enhance the translational utility and our understanding of this endogenous seizure suppressive circuit.

Disclosures: E. Wicker: None. P.A. Forcelli: None.

Poster

041. Epilepsy: Seizure Mechanisms

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Topic: B.10. Epilepsy

Support: NIH/NINDS grant R01-NS096976
NIH/NINDS grant R01-NS103139

Title: Multiple scales network study of epileptiform activity in larval zebrafish using *in vivo* calcium imaging

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Abstract: Epileptic seizures are characterized as a pathological state of hypersynchronous neuronal network activity. Although temporal features of seizure activity are well characterized using electrophysiological techniques, such as electroencephalography and local field potential, these approaches do not capture the network spatial dynamics underlying these events. It is important to understand the pathological changes of network to more precisely define epileptic events, determine underlying triggers and develop new treatments. Efforts to image network activity have largely been limited to microcircuits in brain slices or small “windows” in the rodent’s brain. Here we utilized well-established chemoconvulsant seizure protocols (pentylentetrazole, PTZ; 4-aminopyridine, 4-AP), combined with GCaMP-expressing larval zebrafish and fast *in vivo* confocal microscopy (20-30 Hz acquisition speeds) to image 1) epileptiform activity across the larval zebrafish central nervous system, and 2) individual neuronal activity within the optic tectum microcircuit. Simultaneous local field potential recording was conducted to confirm the correlation between calcium transients and electrographic epileptiform events. A novel image processing pipeline was developed to evaluate synchronization of brain-wide network activity, and the spatiotemporal patterns of individual neuron activity in a local microcircuit. Using *NeuroD:GCaMP6f* expressing larval zebrafish between 5 and 6 days postfertilization (n = 20) we reliably observed 1) electrographic ictal-like events associated with widespread and synchronous activation of neural networks across all major brain regions, and 2) that application of PTZ (10 mM) and 4-AP (4 mM), i.e., drugs targeting different convulsant mechanisms, resulted in distinct network dynamics at both brain-wide and microcircuit scales. Preliminary data uncovered multiple neuronal ensembles, comprised of the coactivation of spatially localized neurons, occurring randomly during interictal-like periods. We predict that these “micro-ensemble” activities could be used to classify a network as epileptic or control. Taken together, these results demonstrate that macro- and micro-network calcium motifs in zebrafish will provide a greater understanding of the network dynamics underlying epileptic seizures.

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Poster

041. Epilepsy: Seizure Mechanisms

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Topic: B.10. Epilepsy

Support: National Science Foundation (NSF-1264948)

Title: Spatial inhomogeneity in burst suppression pattern caused by an acute epileptic focus

Authors: *H. MA¹, E. BAIRD-DANIEL², J.-Y. LIOU³, M. ZHAO⁴, A. G. DANIEL², C. A. SCHEVON³, T. H. SCHWARTZ⁵

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Abstract: Burst suppression (BS) is a pattern of globally symmetric alternating high frequency activity and isoelectricity which can be induced by several forms of anesthesia. There is scattered evidence that BS may become spatially nonuniform in the setting of underlying pathology. We created an epileptic focus in rodent neocortex with focal injection of 4-aminopyridine. BS was induced with isoflurane and events were recorded with wide-field calcium imaging and a multielectrode array. We find that the epileptic focus elicits a rapid alteration in both the triggering, initiation and propagation of BS events. Compared with the non-epileptic brain, events become triggered from the thalamus, initiate in regions uniquely outside the ictal onset zone (IOZ), elicit marked increases in multiunit activity and delay their propagation to the epileptic focus. These findings may be useful clinically as a technique to map the IOZ in patients with severe forms of focal epilepsy in preparation for local therapy.

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Poster

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Topic: B.10. Epilepsy

Support: NIH Grant R01EB019804

Title: Spontaneous seizure-associated spreading depolarization in a chronic rodent model of temporal lobe epilepsy

Authors: *C. M. CURAY¹, F. BAHARI², J. LIU³, J. KIMBUGWE⁴, S. J. SCHIFF⁵, K. D. ALLOWAY⁶, B. J. GLUCKMAN⁷

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Abstract: Spreading Depression (SD) and Seizure dynamics were assumed in older literature to be closely associated, and early acute (evoked) seizure investigations were accompanied by the emission of SD waves (eg. Van Harreveld 1953). There has recently been renewed interest in the link between seizure and SD - including theoretical work implicating that these source from a unified set of instabilities (Wei 2014), and from the hypothesis that Sudden Unexpected Death in Epilepsy is mediated by SD invasion of brainstem (Aiba 2015).

There have been only rare if any observations of spontaneous seizure-associated SD events. We hypothesize this is primarily due to technical/instrumentation limitations. We first observed SD events associated with spontaneous seizures in a murine model of post-cerebral malaria epilepsy (Ssentongo, 2017) with an in-house constructed digital recording system with DC sensitivity, sufficient dynamic range, and non-polarizing electrodes.

Here we report that spontaneous SD events occur frequently in the tetanus toxin model of temporal lobe epilepsy.

We have extended our system to provide 16 channels of biopotential recording plus head acceleration in rats. We utilized this technology for experimental measurements of cortical activity and hippocampal field potentials.

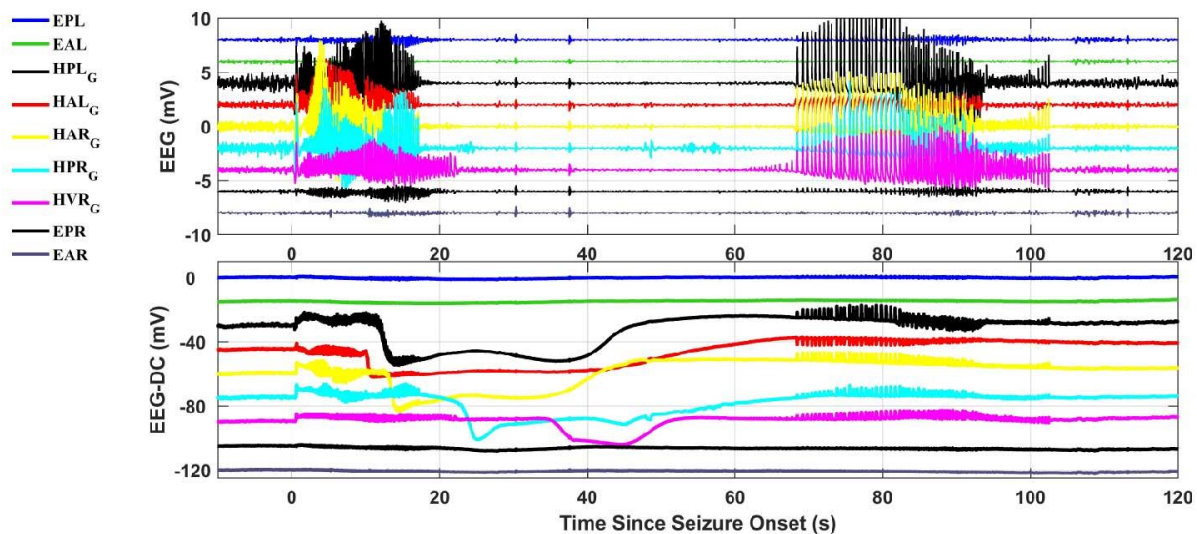
We find that initiation of SD events is linked to the seizure focus and that SD events potentially mediate seizure severity and underlie seizure clusters. These measurements are the first record of spontaneous seizure-related spreading depolarization in an animal model of temporal lobe epilepsy. They provide a platform for mechanistic investigation of seizure-SD dynamics in chronic epilepsy and cases of sudden unexplained death in epilepsy (SUDEP) that may lead to new intervention and treatment approaches.

Van Harreveld, A. (1953). *J. Neurophysiology*, 16(4), 352-366.

Wei, Y., (2014). *J. Neuroscience*, 34(35), 11733-11743.

Aiba, I (2015). *Science Translational Medicine*, 7(282), 282ra46.

Ssentongo, P. (2017). *Scientific reports* 7: 43652.



Disclosures: C.M. Curay: None. F. Bahari: None. J. Liu: None. J. Kimbugwe: None. S.J. Schiff: None. K.D. Alloway: None. B.J. Gluckman: None.

Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 041.16/H13

Topic: B.10. Epilepsy

Support: NIH Grant R01EB019804

Title: Low cost small animal emu suitable for high-fidelity dc-sensitive 24/7 recording

Authors: *J. LIU¹, M. W. BILLARD², A. IMHOF², F. BAHARI³, J. KIMBUGWE², S. J. SCHIFF⁴, K. D. ALLOWAY⁵, B. J. GLUCKMAN⁶

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Abstract: There has been a long-term need for low-cost, highly efficient and high fidelity recording systems for home-cage monitoring of animal models of epilepsy. The uses for such systems spans the establishment and characterization of chronic models of epilepsy and to the investigation of long-term trends of seizure expression, the interaction between sleep and epilepsy, to the assessment of drug interventions for both seizure and epileptogenesis. The need for exhaustive continuous recording can be understood by considering that the likelihood of a false negative diagnosis of epilepsy increases inversely with the base seizure rate, yet the ability to do such classification, and the mechanisms surrounding changes in seizure susceptibility, are critical for the development of clinically relevant treatments.

In previous work, we have developed a low-cost DC sensitive recording system suitable for recording chronically from mice (Ssentongo 2017), based on an earlier design for a low-cost human compatible EEG recording system also from the Gluckman lab (Jain 2011), and utilizes commercial off the shelf (COS) integrated circuit components for the recording system. We recorded from mice with this system for typically weeks to months, with the longest recording lasting nearly 9 months.

We have now extended the design of this system for use in chronic rat recordings. Denoted PSU-EEG RatBoard, the new system is 1"x1"x0.25", plugs into an electrode interface board on the rats head, has 16-channels of biopotential recording and a 3-axis accelerometer. The whole system fits into a small 3D-printed box on a rat's head and is connected to a low-weight USB cable to a commutator at the top of a customized cage. A single-board computer attached to the cage cover acquires data continuously to a network attached storage (NAS) device. A separate

low-light level-compatible camera system similarly spools video data to the same NAS. Each cage's electronics are connected to power and internet via a pair of Power over Ethernet (POE) cables. A full rig - cage, amplifier, commutator, and associated electronics - fits into a standard ventilated cage rack. Additionally, the cage base is a standard autoclave-ready rat cage, and with practice, cages can be changed without interrupting recordings. Individual recording rigs can be duplicated for under \$1000 per rig.

We present here the overall system design, and demonstrate examples of the types of epilepsy and sleep monitoring ongoing from the tetanus toxin model of temporal lobe epilepsy.

Ssentongo, P, et al., Scientific Reports 2017, 7: 43652.

Jain, A, et al., IEEE EMBS, 2011, pp. 1888 - 1891.

Disclosures: **J. Liu:** None. **M.W. Billard:** None. **A. Imhof:** None. **F. Bahari:** None. **J. Kimbugwe:** None. **S.J. Schiff:** None. **K.D. Alloway:** None. **B.J. Gluckman:** None.

Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 041.17/H14

Topic: B.10. Epilepsy

Support: NIH NINDS

Title: Variability in sites of earliest recorded seizure activity in a rat model of temporal lobe epilepsy

Authors: ***P. BUCKMASTER**

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Abstract: How does a seizure start in temporal lobe epilepsy? Possibilities include a single focus, multiple independent foci, or a network of interlinked regions. To address this, variability in sites of earliest recorded seizure activity was measured in rats (n=13) treated systemically with pilocarpine when they were 34-41 d old. 9 ± 1 months later (mean \pm sem) electrodes were directed bilaterally to the septum, amygdala, olfactory cortex, dorsal and ventral hippocampus, ventral subiculum, and medial entorhinal cortex. Signals were obtained (0.1-1800 Hz, 2000 Hz sampling, Neuralynx) \sim 9 h/d, recording continued for 30 ± 4 d, then electrodes were anatomically localized. All 1451 seizures >10 s in duration were analyzed, 112 ± 19 per rat, range 13-186. Blind to electrode site, the channel was identified with the earliest persistent change that developed into clear seizure activity for each seizure. For each recording site in each rat the expected probability of recording earliest seizure activity, assuming random onset sites, was calculated and compared to the observed probability, resulting in a z-score for each site. There were 2.5 ± 0.3 (range 1-4) sites/rat with a significant z-score (i.e., more likely than chance

to display earliest seizure activity). There were early sites on both sides of the brain in 11/13 rats. Including all rats and recording sites the number of early versus all recording sites in the ventral hippocampus was 15/20, 7/21 in ventral subiculum, 4/24 amygdala, 3/23 dorsal hippocampus, 2/17 medial entorhinal cortex, 1/22 olfactory cortex, and 0/16 septum. Individual early sites accounted for $30 \pm 3\%$ (range 8-70%) of seizures/rat. Summing all early sites in each individual rat accounted for $74 \pm 4\%$ (range 47-96%) of seizures. Considering only the site with the maximum z-score in each rat, which accounted for $44 \pm 5\%$ (range 14-70%) of seizures/rat, 54% of maximum z-score sites were in the ventral hippocampus, 15% in ventral subiculum, 15% dorsal hippocampus, 8% amygdala, and 8% medial entorhinal cortex. These findings confirm our previous report that seizures are most likely to be recorded earliest in the ventral hippocampal formation (Toyoda et al., 2013), which is homologous with the anterior hippocampus in humans. Constraints on spatial sampling resolution with local field potential recordings are limiting. Nevertheless, variability in early sites seems more consistent with multiple foci or a network of interlinked seizure-initiating regions than with a single focus. Better knowledge of how seizures start might lead to more precise treatments for patients with temporal lobe epilepsy.

Disclosures: P. Buckmaster: None.

Poster

041. Epilepsy: Seizure Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 041.18/H15

Topic: B.10. Epilepsy

Support: KHIDI Grant HI15C2854
NRF Grant NRF-2017R1D1A1B03029812

Title: Blocking hippocampal apolipoprotein D after acute seizures prevents cognitive impairment associated with epilepsy

Authors: J.-E. KIM¹, *K. CHO²

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Abstract: Epileptic seizures can induce structural and molecular alterations of granule cells in the dentate gyrus, which can lead to epilepsy-associated cognitive impairment. However, the molecular mechanisms contributing to memory deficits are still not fully understood. To identify actively translated mRNAs in mature granule cells after status epilepticus (SE), we injected pilocarpine to 6 weeks old of neurotrophin-3 driven BAC-TRAP (bacterial artificial chromosome-translating ribosome affinity purification) transgenic mice. From RNA-seq analysis, we identified several candidate genes including apolipoprotein D (ApoD) of which expression was significantly increased at 8 days after acute seizures. We verified ApoD

upregulation at 3 and 7 days after SE in the hippocampus of C57BL/6 and FACS-sorted dentate granule cells of Prox1-GFP mice by Western blot analysis. Moreover, we found increased filipin staining in the hippocampal neuronal cultures after applying Mg²⁺ free medium, suggesting increased cholesterol level after acute seizures. When hippocampal ApoD was silenced with multiple siRNA injections, ApoD expression was markedly reduced throughout the latent period. At 4 weeks after acute seizures, C57BL/6 mice were subjected to novel location (NL) recognition tests. Compared to control siRNA-treated animals, mice with ApoD knockdown showed a significant higher preference ratio in NL test, indicating memory function spared in epilepsy. Taken together, our findings suggest that hippocampal modulation of ApoD after acute seizures can ameliorate epilepsy-associated memory impairment, possibly via the regulation of cholesterol metabolism.

Disclosures: J. Kim: None. K. Cho: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.01/H16

Topic: B.11. Glial Mechanisms

Support: NSERC Discovery Grant

Title: Regional characterization of vimentin-immunoreactive astrocytes in the human brain

Authors: *L. A. O'LEARY^{1,2}, C. BELLIVEAU^{1,2}, M. DAVOLI¹, N. MECHAWAR^{1,2,3}

¹McGill Group For Suicide Studies, Douglas Inst., Verdun, QC, Canada; ²Integrated Program in Neurosci., ³Dept. of Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: Introduction: This study aims to characterize the distribution and morphology of astrocytes in various human brain regions. Astrocytes are commonly identified by their expression of glial fibrillary acidic protein (GFAP), an intermediate filament protein. However, GFAP-immunoreactive (GFAP-IR) astrocytes constitute only a subset of astrocytes in the normal, healthy brain, leaving most cells unscrutinized. We hypothesized that vimentin, another intermediate filament protein expressed by glia, would label complementary subsets of astrocytes. To test this hypothesis, we performed fine neuroanatomical analyses on vimentin- and GFAP-immunoreactive (-IR) astrocytes in well-characterized postmortem human brain samples (n=5 healthy individuals) provided by the Douglas-Bell Canada Brain Bank. Methods: Fresh-frozen tissue from the prefrontal and occipital cortex, caudate nucleus, and mediodorsal thalamus was postfixed and immunostained for brightfield (single labeling) or immunofluorescence (double labeling) using anti-vimentin and anti-GFAP antibodies. Densities and morphometric properties of astrocytes were examined using *StereoInvestigator* and *Neurolucida* (MBF

Bioscience). Results: The quantity and morphology of vimentin-IR astrocytes was similar in all examined regions except for the thalamus, in which only a few cells were observed. These cells were generally found to contact vimentin-IR blood vessels. Overall, only a minority (10%) of vimentin-IR astrocytes were also GFAP-IR. Discussion: Double-labeling immunohistochemical results suggest that in the human brain, vimentin-IR astrocytes are mostly distinct from GFAP-IR astrocytes. This is further supported by the relative inter-regional morphological homogeneity of vimentin-IR astrocytes, which contrasts with previous reports of highly distinct GFAP-IR astrocytic subtypes in the human brain. The functional implications of these findings are currently being investigated.

Disclosures: L.A. O'Leary: None. C. Belliveau: None. M. Davoli: None. N. Mechawar: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.02/DP03/H17

Topic: B.11. Glial Mechanisms

Support: F32 NS100335-02 (NINDS)
R01 MH099544 (NIMH)
R03 DA042480-01A1 (NIDA)

Title: Astroglial contributions to sleep homeostasis

Authors: *A. M. INGIOSI, C. R. HAYWORTH, D. O. HARVEY, J. P. WISOR, M. G. FRANK

Biomed. Sci., Washington State Univ., Spokane, WA

Abstract: Insufficient sleep is an epidemic that poses significant clinical and economic impacts. Poor sleep can be caused by impaired sleep homeostasis which regulates sleep need as a function of prior wakefulness. The biological substrates of sleep homeostasis are incompletely understood. Therefore, determining the cellular basis of sleep homeostasis is necessary to understand underlying causes of abnormal sleep. Astrocytes may play a central role. Astrocytes are found throughout the brain and modulate compensatory responses to sleep loss. Because astroglial chemical signaling is mediated by changes in intracellular calcium, we hypothesize that astroglial intracellular calcium dynamics contribute to the accumulation and discharge of sleep need. To test this hypothesis, we characterized astroglial calcium signals in spontaneous sleep and in response to sleep deprivation. Intracellular calcium activity was captured *in vivo* using a head-mounted epifluorescent microscope in unanesthetized, freely-behaving mice expressing the genetically encoded calcium indicator GCaMP6f selectively in astrocytes of the

frontal cortex. Astroglial calcium dynamics were simultaneously recorded with sleep-wake behavior as determined by electroencephalography and electromyography. Adult male C57Bl/6J mice (n = 6; 10 – 14-weeks-old) underwent a counterbalanced design of 24 h undisturbed baseline recording as well as 6 h of sleep deprivation via gentle handling followed by 18 h recovery sleep. Current data show that astroglial calcium signals increase after sleep deprivation (i.e. high sleep need) and decrease as mice are allowed to sleep (i.e. low sleep need). These changes in calcium activity positively track with changes in delta power in non-rapid eye movement (NREM) sleep, a standard index of sleep need. Data also indicated that astroglial calcium dynamics are generally higher during wakefulness and lower during NREM and REM sleep. Overall, astroglial calcium activity 1) changes with sleep need, and 2) changes with arousal state. These studies are the first to describe astroglial calcium activity in conjunction with electroencephalographic determination of arousal state.

Disclosures: A.M. Ingiosi: None. C.R. Hayworth: None. D.O. Harvey: None. J.P. Wisor: None. M.G. Frank: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.03/H18

Topic: B.11. Glial Mechanisms

Support: HI14C1913

HI15C0527

NRF-2016R1E1A1A01941212

2017M3C7A1028949

Title: Nitric oxide-induced TFEB activation in murine cortical astrocytes requires zinc release from metallothionein-3

Authors: *B.-R. SEO¹, J. CHOI¹, Y.-H. HAN¹, J.-Y. KOH^{1,2}

¹Neural Injury Res. Ctr., Asan Inst. for Life Sci., Seoul, Korea, Republic of; ²Department of Neurol., Asan medical center, Seoul, Korea, Republic of

Abstract: In cultured astrocytes, oxidative or nitrative stress induces zinc release from metallothioneins (Mt) especially Mt3, which may mediate diverse intracellular changes including autophagy. Transcription factor EB (TFEB) is a master switch to turn on the CLEAR network genes. Nuclear translocation of TFEB works to increase levels of autophagy-related proteins and lysosomal proteins, augmenting autophagic flux and lysosomal degradation. Hence, in the present study, we examined whether nitric oxide activated TFEB in cultured astrocyte, and determined the role of intracellular zinc release herein.

Upon exposure to subtoxic levels of SNOG (0.5-1 mM), intracellular levels of free zinc rapidly rose in wild-type (WT) astrocyte. However, in astrocytes cultured from Mt3 KO mice, although their NO levels upon SNOG exposure were approximately the same as those of WT astrocytes, free zinc levels hardly increased from the baseline. Next, we examined TFEB expression in these cells. Whereas in WT astrocyte SNOG induced translocation of TFEB to nucleus, in Mt3 null astrocytes, it failed to do so. Western blots for TFEB of nuclear fractionation confirmed this finding. Hence, we wondered whether there is a mechanical link between zinc release and TFEB activation in astrocytes. First, we increase cytosolic zinc levels by using a zinc ionophore Zn-Clioquinol in Mt3 null astrocyte. This maneuver successfully induced TFEB translocation to nuclei. Second, conversely, when we treated WT astrocyte with a cell-permeant zinc chelator TPEN, both intracellular rises of free zinc and the TFEB translocation to nuclei were blocked. These results supported the hypothesis that cytosolic zinc release from Mt3 plays a crucial role in NO-induced TFEB activation in astrocyte. As expected, TFEB activation following SNOG exposure resulted in increases in autophagy flux as evidenced by an increase in LC3-II and a decrease in p62 levels. These changes were not seen in Mt3 null astrocyte treated with SNOG, but addition of Zn-Clioquinol that restored TFEB activation, also increased autophagy flux. Present results in astrocytes show that NO activates TFEB via intracellular zinc release. The main source of NO-triggered zinc release in astrocytes appears to be Mt3, a CNS-enriched form. Since zinc can participate in diverse signaling processes, it appears plausible that at least some of NO-mediated changes in brain cells is mediated by zinc release from Mt3.

Disclosures: B. Seo: None. J. Choi: None. Y. Han: None. J. Koh: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.04/I1

Topic: B.11. Glial Mechanisms

Title: Calcium oscillation increase in the hippocampal astrocytes induced by sonic hedgehog

Authors: *C. ADACHI¹, S. ARAI², T. KITAGUCHI², S. TAKEDA³, T. INOUE¹

¹Life Sci. and Med. Biosci., Waseda Univ., Tokyo, Japan; ²Waseda Biosci. Res. Inst. in Singapore (WABIOS), Singapore, Singapore; ³Anat. and Cell Biol., Yamanashi Univ., Yamanashi, Japan

Abstract: Sonic Hedgehog (Shh) plays a key role in organogenesis and patterning in development. In the adult central nervous system (CNS), Shh is expressed in hippocampal dentate gyrus and the subventricular zone and involved in the retention, proliferation and differentiation of neural stem cells. Patched, receptor of Shh, and Smoothed, downstream of patched, are also expressed in the entire hippocampal area, and Shh is reported to present in the

hippocampal synapses. Thus it was expected that hippocampal cells respond to Shh. We report here that Shh and SAG, a Smoothened agonist, increased calcium oscillation frequency in cultured hippocampal astrocytes. Involvement of calcium signaling has not been known in the Shh signaling pathway. The response started within several minutes after stimulation. This rapid response suggested that a non-canonical pathway was operating, because the canonical pathway of Shh requires hours to take effect through modulation of transcription. Pertussis toxin blocked the enhancement of calcium oscillation frequency by SAG, suggesting that G_i is linked to Smoothened. Accordingly, a cAMP indicator protein, Flamingo 2, reported decreases in cAMP and an ATP indicator protein, MaLion G, reported increase in ATP by SAG stimulation. Extracellular ATP depletion by an ATP degrading enzyme, apyrase, inhibited the increase in calcium oscillation frequency by SAG. MaLion G reported steep decreases in ATP concentration in astrocytes, which was thought to reflect ATP release. The frequency of rapid ATP concentration decrease was increased by SAG. The SAG-activated calcium oscillation was not affected by removing extracellular calcium, but inhibited by 2-APB, an IP_3 receptor antagonist, and thapsigargin, an inhibitor of ER Ca^{2+} -ATPase. Altogether, we propose the following scenario: Shh activates Smoothened-coupled G_i which reduces conversion of ATP to cAMP. ATP release from astrocytes is enhanced, which activates $G_{q/11}$ -coupled P2Y receptors on astrocytes, leading to activation of IP_3 -mediated calcium oscillation. Shh secretion in the adult CNS is well known in injury, where astrocytes become reactive and form scar. The activation of calcium oscillation by Shh observed in this study might be related to transformation of astrocytes upon tissue injury.

Disclosures: C. Adachi: None. S. Arai: None. T. Kitaguchi: None. S. Takeda: None. T. Inoue: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.05/I2

Topic: B.11. Glial Mechanisms

Support: NIH-NIDA (1F30DA042510-01) to MC
NIH-NINDS (R01NS097312-01) to AA
Human Frontier Science Program (Research Grant RGP0036/2014) to AA

Title: Astrocytes contribute to dopamine signaling in the nucleus accumbens

Authors: *M. CORKRUM¹, A. COVELO², R. QUINTANA², M. THOMAS³, A. ARAQUE⁴
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Abstract: Astrocytes have classically been considered support cells of the brain. However, although astrocytes are not electrically excitable, astrocytes respond to neurotransmitters with cytoplasmic Ca²⁺ elevations, which, in turn, can trigger the release of neuroactive substances, leading to the modulation of synaptic transmission and plasticity. Whether astrocytes respond to dopamine and the physiological consequences of this activation remain largely unknown. We have investigated the effects of dopamine and amphetamine on astrocyte calcium signals and its consequences on excitatory synaptic transmission in the nucleus accumbens. We combined calcium imaging with selective optogenetic stimulation of dopaminergic terminals to investigate astrocytic responsiveness to dopamine. To determine the consequences of astrocyte activation on synaptic transmission we performed electrophysiological recordings of excitatory post synaptic currents and activated astrocytes with selective optogenetic stimulation of dopaminergic axons and by activating Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) specifically expressed in astrocytes. We found that astrocytes respond to synaptically-released dopamine and amphetamine-induced dopamine elevations with increases in cytoplasmic Ca²⁺ in both the somas and processes. These dopamine-induced Ca²⁺ elevations in astrocytes were associated with a depression of excitatory synaptic transmission through activation of adenosine A₁ receptors. When astrocyte Ca²⁺ signals were ablated, the dopamine-evoked depression of excitatory transmission was no longer observed, suggesting that intact astrocyte Ca²⁺ is necessary for this phenomenon. Furthermore, specific activation of astrocytes with DREADDs resulted in a depression of synaptic transmission that mimicked the dopamine-mediated synaptic depression, indicating that astrocyte Ca²⁺ elevations are sufficient to depress excitatory transmission in the nucleus accumbens. Present results indicate that astrocytes in the nucleus accumbens regulate dopamine-evoked depression of excitatory transmission and may serve as potential therapeutic targets for diseases involving dysregulated dopamine signaling.

Disclosures: M. Corkrum: None. A. Covelo: None. R. Quintana: None. M. Thomas: None. A. Araque: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.06/I3

Topic: B.11. Glial Mechanisms

Support: CIHR Foundation Grant

Title: Piezo1 is a novel calcium entry pathway in astrocytes

Authors: *L. E. WICKI-STORDEUR, R. W. KO, N. L. WEILINGER, B. A. MACVICAR
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Abstract: Astrocytes are critical players in the regulation and support of various brain functions, including neuronal activity, synaptic plasticity and blood flow. While electrically unexcitable, the intracellular calcium levels within astrocytes show dramatic fluctuations in ‘wave’ and ‘spark’-like patterns, which are believed to modify astrocyte function. Our lab demonstrated that calcium sparks within the fine processes of astrocytes were largely dependent on calcium influx from the extracellular space, rather than release from internal stores; however, the route of this calcium entry was not identified. Here we uncover a novel calcium entry mechanism in astrocytes. We show that Piezo1, a mechanosensitive cation channel, is expressed in astrocytes, both in primary culture and within the brain. Piezo1 expression decreases with age, and rebounds in astrocytes following tissue damage. Using pharmacological and genetic manipulations of Piezo1 function, we demonstrate that this channel contributes to astrocyte calcium sparks. Piezo1 activation also increases release of the gliotransmitter ATP, and modulates downstream signaling networks. Our work identifies a novel player in astrocyte calcium signaling and contributes to understanding the importance of this phenomenon within the brain.

Disclosures: L.E. Wicki-Stordeur: None. R.W. Ko: None. N.L. Weilinger: None. B.A. MacVicar: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.07/I4

Topic: B.11. Glial Mechanisms

Support: NIH Grant F31NA100259

Title: Neuronal BDNF contributes to astrocyte morphogenesis through astrocytic TrkB.T1

Authors: *L. HOLT^{1,2}, N. L. PACHECO³, M. L. OLSEN¹

¹Sch. of Neurosci., Virginia Tech., Blacksburg, VA; ²Cell, Developmental, and Integrative Biol., Univ. of Alabama at Birmingham, Birmingham, AL; ³Cell, Developmental, and Integrative Biol., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Birth of astrocytes during early postnatal development in rodents is followed by a period of morphological maturation including the development and extension of fine dense processes, which eventually enwrap synapses and blood vessels. The developmental time window of astrocyte morphological maturation and refinement is well defined, but the molecular mechanisms that underlie this process are not well understood. Brain derived neurotrophic factor (BDNF) is a critical growth factor secreted largely by neurons and involved in the development and maturation of neurons, including neuronal growth and synapse refinement. In the current study we demonstrate that astrocytes express high levels of the BDNF receptor TrkB when

compared to neurons, and is in fact one of the most abundant mRNA's expressed in astrocytes. RNA Sequencing and qPCR data indicate astrocytes predominantly express the truncated isoform of TrkB, TrkB.T1, which lacks the canonical kinase domain. TrkB.T1 expression is highest in astrocytes during astrocyte morphological refinement and maturation, a developmental time window that coincides with the highest neuronal BDNF mRNA expression levels. These findings have led us to hypothesize that BDNF/TrkB.T1 signaling is an important mediator of astrocyte morphological maturation. Here we utilize a novel serum-free astrocyte culture paradigm to analyze *in vitro* astrocyte morphology, and demonstrate that exposure to 30ng BDNF leads to a 2-fold increase in astrocyte complexity. Loss of the TrkB.T1 receptor prevents BDNF-induced increases in morphology *in vitro*, and *in vivo* astrocytes demonstrate a 30% reduction in total volume. Additionally, Sholl analysis demonstrates reduced astrocytic process complexity with no change in process length in TrkB.T1 knockout animals. Furthermore, preliminary experiments demonstrate neurons cultured in the presence of TrkB.T1 KO astrocytes exhibit decreased numbers of excitatory and inhibitory synapses, suggesting BDNF/TrkB.T1 signaling in astrocytes contributes to neuronal synapse development. Ongoing studies are aimed at understanding the relative importance of BDNF/TrkB.T1 signaling in astrocyte morphological maturation and functional consequences on neuronal synapses and function.

Disclosures: L. Holt: None. N.L. Pacheco: None. M.L. Olsen: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.08/I5

Topic: B.11. Glial Mechanisms

Support: NINDS R01NS075062
NHLBI R01HL104101

Title: Kir4.1-like currents contribute to the development of unique regional astrocyte Co₂/H⁺sensitivity in the retrotrapezoid nucleus

Authors: K. PATTERSON¹, C. M. GONÇALVES², D. K. MULKEY³, *M. L. OLSEN⁴
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Abstract: Evidence indicates that retrotrapezoid nucleus (RTN) astrocytes sense changes in tissue CO₂/H⁺ to mediate breathing alterations; however, the mechanism(s) by which they do so remain unclear. Alterations in inward K⁺ currents and the astrocyte cell membrane potential represent candidate means by which CO₂/H⁺ signals may be conveyed to neurons. Here, we use

slice electrophysiology in rats of either sex to show that RTN but not cortical astrocytes intrinsically respond to CO₂/H⁺ by inhibition of Kir4.1-like currents, an effect that increases developmentally and parallels robust upregulation of Kir4.1 and Kir5.1 protein. Kir4.1 blockade by Ba²⁺ is sufficient to mimic the effect of CO₂/H⁺ exposure in the RTN as measured by reductions in astrocyte Kir4.1-like currents as well as increases in neural firing. These data suggest that Kir4.1 inhibition by CO₂/H⁺ may govern the degree to which astrocytes mediate downstream chemoreceptive signaling events through cell-autonomous mechanisms as well as by amplifying the RTN neural intrinsic response to CO₂/H⁺. These results identify Kir4.1 channels as potentially important regional CO₂/H⁺ sensors early in development, thus expanding our understanding of how astrocyte heterogeneity may uniquely support specific neural circuits.

Disclosures: **K. Patterson:** None. **C.M. Gonçalves:** None. **D.K. Mulkey:** None. **M.L. Olsen:** None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.09/I6

Topic: B.11. Glial Mechanisms

Support: FONDECYT 1140108

CONICYT-PCHA/Doctorado Nacional/2015-21150958

Title: Protein SUMOylation determines the cargo content of astrocyte-derived small extracellular vesicles

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¹CIB, Univ. De Los Andes, Las Condes, Chile; ²Univ. Austral, Valdivia, Chile

Abstract: Small extracellular vesicles (sEVs) including exosomes are secreted by most cells to the extracellular milieu after fusion of endosomal compartments with the cell membrane. The molecular content of sEVs (lipids, proteins and nucleic acids) depends on the cell type of origin and on its physiological state. In that line, possible post-translational modifications that regulate loading of a specific protein cargo in to sEVs are incompletely understood. Here, we studied whether conjugation with SUMO (Small Ubiquitin-like Modifier) can serve as a signal that determines the cargo of sEVs. We used primary cultures of astrocyte and HeLa cultures expressing 6His-SUMO1 and 6His-SUMO2, to isolate EVs by sequential ultracentrifugation, mass spectrometry, in silico analysis (Gene Ontology, GeneCodis and Panther) and Western Blot. To show the in vivo relevance of SUMO conjugation, we isolated sEVs from the plasma of rats (that are partly derived from glial cells).

We found that SUMO1 or SUMO2 expressing cells release a differential proteome within sEVs.

In the case of SUMO1, the analysis indicates primarily regulation of protein translation while in the case of SUMO2, the catalytic activity of catabolic enzymes. In plasma sEVs, SUMOylated form of the glycolytic enzyme Aldolase C (a protein contained in astrocyte sEVs) was detected. These results are compatible with a differential role of SUMO1 and SUMO2 conjugation that has functional implications in the cargo determination of sEVs derived from glial cells.

Disclosures: A. Fernández: None. O. Santis: None. A. Rojas: None. U. Wyneken: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.10/I7

Topic: B.11. Glial Mechanisms

Support: National Institute of Neurological Disorders and Stroke R01NS052741
RG3367 from the National Multiple Sclerosis Society

Title: The proteolytic microenvironment as a regulator of astrocyte form and function

Authors: *S. SLADE^{1,2}, H. YOON^{2,3}, M. RADULOVIC^{1,2}, W. SIMON^{1,2}, I. A. SCARISBRICK^{1,2,3}

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Abstract: The central nervous system is rich in serine proteinases, with kallikrein-related peptidase 6 (KLK6) being among the most abundant (Scarisbrick et al., 1997). Despite an expanding research field pointing to deregulation of serine proteinases in injury and disease, including Alzheimer's and Parkinson's disease, frontotemporal dementia, multiple sclerosis, and traumatic injury, little is known regarding their physiological or pathophysiological roles and mechanisms of action. Kallikreins are a family of 15 secreted serine proteases that comprise the largest contiguous cluster of serine proteases in the human genome. KLK6 is abundant in mature oligodendrocytes and neurons of the intact brain and spinal cord and is upregulated in astrocytes and microglia in the context of injury or disease. Studies emerging from our laboratory suggest that KLK6 can signal in a hormone-like fashion to regulate neural cell behavior by cleaving and thereby activating select protease activated receptors (PARs). PARs have seven transmembrane helices coupled to intracellular heterotrimeric G proteins. Proteolytic activation unmasks a new tethered peptide sequence that folds back onto the PAR, serving as a ligand to elicit intracellular signaling. There are 4 PARs (PAR1-4) and each is expressed at significant levels across the brain and spinal cord. In this study, we used a combination of recombinant KLK6 protein and primary murine astrocytes derived from the cortex of postnatal wild type mice or mice with genetic knockout of PAR1 or PAR2 to gain insights into how KLK6 regulates astrocyte biology. First,

we demonstrate that recombinant KLK6 evokes increases in intracellular Ca^{2+} in primary murine astrocyte monolayer cultures via activation of PAR1. In addition, KLK6 promoted a condensation of astrocyte cortical actin leading to an elongated stellate shape and multicellular aggregation in a manner that was dependent on the presence of either PAR1 or PAR2. KLK6-mediated changes in astrocyte shape were accompanied by translocation of β -catenin from the plasma membrane to the cytoplasm and an increase in secretion of interleukin 6, each in a manner dependent on the presence of PAR1 or PAR2. These data are exciting because they demonstrate that KLK6 can influence astrocyte plasticity through receptor-dependent mechanisms. Furthermore, this study expands our understanding of the mechanisms by which kallikreins can contribute to neural homeostasis and remodeling and point to both PAR1 and PAR2 as new therapeutic targets to modulate astrocyte form and function.

Disclosures: S. Slade: None. H. Yoon: None. M. Radulovic: None. W. Simon: None. I.A. Scarisbrick: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.11/I8

Topic: B.11. Glial Mechanisms

Title: The evolutionary origin(s) of glia

Authors: *D. K. HARTLINE

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Abstract: If broadly defined as non-neuronal cell types of typically ectodermal origin that are intimately associated with neurons, "glia" can be identified in the nervous systems of all advanced bilaterians, with a list of known key functions that is constantly growing. The purpose of this study was to further elucidate the evolutionary origin of glia as an aid to understanding both the constraints on its subsequent evolutionary trajectories and, if independent origins can be identified, the functions giving rise to the original innovation. Such functions may differ substantially from those in more advanced nervous systems. Inferences about where in evolution this cellular innovation has emerged are in flux owing to the rapidly-changing understandings of phylogenetic relationships. The present study surveys the evidence based on current phylogenies and taxonomic coverage of organisms that have been specifically examined for glial presence based on morphological characters. A recent reassignment to the base of bilaterian phylogeny for the primitive flat-worm phylum Xenacoelomorpha, some of which possess glia, opens the possibility that this glia is ancestral to all. However, glia is questionable or absent in basal taxa of several other major phyletic lines, raising the possibility that the particular glias in those lines were independently evolved. Overall analysis of current phylogenetic and morphological

evidence is consistent with the hypothesis that glia has arisen as many as five times: as derived characters within the Xenacoelomorpha and the Platyhelminthes (flat worms), and as basal characters of the Ecdysozoa (arthropods and round worms), the Lophotrochozoa (annelids and molluscs), and Deuterostomia (echinoderms and chordates). These conclusions may be expected to need modification as phylogenetic relationships are further refined and as more taxa are examined for glia-like cell types.

Disclosures: D.K. Hartline: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.12/I9

Topic: B.11. Glial Mechanisms

Support: American Association of Endodontists
Canadian Academy of Endodontics
Alpha Omega Foundation Canada
Department of Endodontic Research Grant
AAE/Dentsply Sirona Resident Award

Title: Morphological characteristic of astroglial processes in thick sections of the rat orofacial sensory-motor cortex: Effects of endodontic treatment versus tooth extraction

Authors: *L. AVIVI-ARBER¹, J. LOPEZ GROSS², M. ZANJIR², I. YONA², J. HWANG HO², B. BASRANI², P. CHERKAS¹

¹Univ. of Toronto Dent., Toronto, ON, Canada; ²Univ. of Toronto, Toronto, ON, Canada

Abstract: Rational: The orofacial primary sensory-motor cortex (oSM) is the main brain region involved in generating and modulating orofacial motor functions. Sensory inputs from teeth are crucial in modulating oSM motor outputs and related orofacial motor functions. Astroglial cells closely interact with neurons in the brain. While the functional integrity of astroglia is critical for modulating neuronal function and oSM motor output, altered neuronal activity can induce changes in astroglial morphological features. **Objective:** To use the novel CLARITY technique to render the oSM optically transparent, and immunofluorescence labelling to quantify morphological features of oSM astroglia, and test the **hypothesis** that endodontic treatment vs. tooth extraction induces differential changes in astroglial morphological features. **Methods:** Male *Sprague-Dawley* rats (175-200 g) were randomly allocated into 4 groups (n=5): Endodontic and Extraction groups received, respectively, pulpectomy or extraction of three right maxillary molars under general/local anesthesia; Sham group received anaesthesia and mouth opening; and Naïve group received no treatment. Rats were perfused on postoperative day 7. Brains were

passively cleared. oSM coronal sections (2 mm) were immunolabelled with anti-gial fibrillary acidic protein (GFAP, astroglial marker). Zeiss Lightsheet microscope (20x) was used to acquire 3D-Z-stack images (0.2 x 0.5 x 1 mm³) of oSM layers 1 and 5. Bitplane Imaris software was used for automatic quantification of the volume, surface area, diameter, and straightness of astroglial filaments. Statistical analysis: Repeated-measures ANOVA and *post-hoc* Duncan test as appropriate ($p < 0.05$). **Results:** Significant differences in the morphological features of astroglial filaments were observed between oM and oS and layer 1 and layer 5. A dense network of GFAP-labelled astroglial processes demarcated layer 1 and to a lesser extent layer 5. As compared with control groups, pulpectomy and tooth extraction produced differential changes in the volume and surface area of astroglial processes in oS and oM. **Conclusions/ significance:** Astroglial morphology is region-specific. Endodontic treatment vs. tooth extraction induces differential changes in astroglial morphological features. Future studies will explore whether astroglia can be targeted as a novel therapeutic approach in order to improve sensory-motor recovery following dental injury and treatment.

Disclosures: L. Avivi-Arber: None. J. Lopez gross: None. M. Zanjir: None. I. Yona: None. J. Hwang ho: None. B. Basrani: None. P. Cherkas: None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.13/I10

Topic: B.11. Glial Mechanisms

Support: JSPS Grant 15K15532 (HI-K)

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Waseda University Grants for Special Research Projects 2013B-168 and 2017B-238 (TI)

Title: Characteristics of astrocytic endfeet in mouse brain revealed by laser ablation

Authors: *H. KUBOTERA¹, H. IKESHIMA-KATAOKA¹, Y. HATASHITA¹, A. ALLEGRA MASCARO^{2,3}, F. S. PAVONE², T. INOUE¹

¹Waseda Univ., Tokyo, Japan; ²European Lab. for Non-linear Spectroscopy, Univ. of Florence, Florence, Italy; ³Neurosci. Institute, Natl. Res. Council, Pisa, Italy

Abstract: Astrocytes, a type of glial cell, are the most abundant cell type in the central nervous system and serve many functions, such as provision of nutrients to neurons, control of extracellular pH and uptake of neurotransmitters. In addition, astrocytes contact with blood

vessels via astrocytic endfeet which play important roles including control of blood flow and maintenance of blood-brain barrier (BBB) integrity. Functions of astrocytes have been analyzed by removal of entire astrocytes genetically or pharmacologically, which was not sufficient to gain insights into the specific functions of astrocytic endfeet *per se*. We performed laser ablation on astrocytic endfeet covering blood vessels and *in vivo* imaging with a two-photon laser scanning microscope (2-PLSM) to investigate the functional roles of astrocytic endfeet on the blood vessel. The laser ablation with 2-PLSM enabled focal damages with a high spatial precision, which removed only astrocytic endfeet without visible damages to blood vessels and other astrocytes. Adult transgenic mice expressing EGFP in astrocytes driven by the glial fibrillary acidic protein promoter were used. Blood vessels were labeled with intraperitoneally injected Evans Blue. After specific removal of astrocytic endfeet covering blood vessels, we observed re-cover of the stripped blood vessels by the same or other astrocytic endfeet within a few days. The re-covering by astrocytic endfeet was irrelevant to life or death of ablated astrocytes and the ablated loci, i.e. endfeet or stalks of the astrocytic process. In the half cases of endfoot re-covering blood vessels, endfeet that had already been touching the target blood vessels extended themselves to re-cover the stripped blood vessels. Furthermore, dislocation of astrocytic endfeet from blood vessels did not cause Evans Blue leakage from blood vessels, i.e. BBB was not disrupted. The active restoration of the cover of blood vessels by astrocytic endfeet suggests that the endfeet cover may have physiological importance, although the endfoot cover is not involved in the immediate physical barrier of BBB.

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Poster

042. Astrocyte Biology

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Program #/Poster #: 042.14/I11

Topic: B.11. Glial Mechanisms

Support: R01 NS078331

Title: Modeling the variability of spontaneous astrocyte calcium activity and responses to repeated stimuli

Authors: *M. TAHERI¹, A. D. DORVAL², J. A. WHITE³

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Abstract: Astrocytes, a major glial cell type, communicate bidirectionally with neurons and play several key roles in the brain, many of which are regulated by intracellular Ca²⁺ signaling. We

showed in our recent experimental and computational work that astrocyte Ca^{2+} transients evoked by a single, focal application of ATP are temporally heterogeneous due to specific variability in the biological mechanisms underlying the Ca^{2+} transients. Here, we examine astrocyte Ca^{2+} activity in response to multiple deliveries of ATP, to assess how they may respond to ongoing neuronal activity and what their Ca^{2+} dynamics under different experimental conditions may reveal about the inputs they are receiving.

We use two-photon microscopy to measure Ca^{2+} activity in mouse cortical astrocytes expressing the genetically-encoded Ca^{2+} indicator GCaMP5G. We evoke Ca^{2+} activity through brief (60 ms), focal applications of ATP with varying application time intervals (from 15 s to 4 min). We find that Ca^{2+} transients in response to multiple presentations of ATP stimuli are much more variable than responses to single presentations of ATP. This added variability arises mainly from interactions related to the timing of repeated stimuli, temporally heterogeneous Ca^{2+} responses to each stimulus, and spontaneous Ca^{2+} activity.

We hypothesize that the stochasticity of astrocyte Ca^{2+} events can be described by a Markovian process and that the difference between spontaneous and evoked activity arises from differences in transition rates between the hidden states of a Hidden Markov Model (HMM). By examining the Ca^{2+} features, we find that it is reasonable to simplify the data to two observable states (On and Off). Using these simplified Ca^{2+} traces, we estimate transition rates for multiple HMMs and compare the results from each model to experimental data (both spontaneous and evoked). We find that the simplest model that reproduces our experimental results consists of 3 states (one Off/Closed state and two On/Open states). Next, we hypothesize that during multiple ATP stimulations, the HMM transition rates switch from spontaneous to evoked levels and back, and that changes in Ca^{2+} activity with repeated stimulations can be modeled by incorporating a refractory period in this switch. We use the model to make predictions about the Ca^{2+} responses for each stimulation protocol (e.g. the probability of a cellular region being On at any given time during the recording) and confirm these predictions in the experimental data. Our work provides insight into the heterogeneity of spontaneous and evoked astrocyte Ca^{2+} activity, and provides a tool for studying Ca^{2+} responses under various experimental conditions.

Disclosures: M. Taheri: None. A.D. Dorval: None. J.A. White: None.

Poster

042. Astrocyte Biology

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Topic: B.11. Glial Mechanisms

Support: Swedish Medical Research Council (11548)

ALF Gothenburg (146051)

Söderbergs Foundations

Hjärnfonden
EuroCellNet COST Action

Title: Nestin regulates neurogenesis through notch signaling from astrocytes to neural stem cells

Authors: *M. PEKNA¹, U. WILHELMSSON¹, I. LEBKUECHNER¹, R. LEKE¹, P. MARASEK¹, X. YANG¹, D. ANTFOLK², M. CHEN¹, P. MOHSENI³, E. LASIC⁴, S. TRKOV BOBNAR⁴, M. STENOVEC⁴, R. ZOREC⁴, A. NAGY^{3,4}, C. SAHLGREN^{2,3}, M. PEKNY^{1,2}
¹Univ. of Gothenburg, Gothenburg, Sweden; ²Abo Akademi Univ., Turku, Finland; ³Lunenfeld-Tanenbaum Res. Inst., Toronto, ON, Canada; ⁴Univ. of Ljubljana, Ljubljana, Slovenia

Abstract: The intermediate filament (nanofilament) protein nestin is a marker of neural stem cells, but its role in neurogenesis, including adult neurogenesis, remains unclear. Here, we investigated the role of nestin in neurogenesis in adult nestin-deficient (*Nes*^{-/-}) mice. We found that the proliferation of *Nes*^{-/-} neural stem cells was not altered, but neurogenesis in the hippocampal dentate gyrus of *Nes*^{-/-} mice was increased. Surprisingly, the pro-neurogenic effect of nestin deficiency was mediated by its function in the astrocyte niche. Through its role in Notch signaling from astrocytes to neural stem cells, nestin negatively regulated neuronal differentiation and survival; however, its expression in neural stem cells was not required for normal neurogenesis. In behavioral studies, nestin deficiency in mice did not affect associative learning but was associated with impaired long-term memory.

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.16/DP02/I13

Topic: B.11. Glial Mechanisms

Support: BBSRC

Title: Astrocytes are cellular and molecular targets of lithium treatment: A novel role for lysyl oxidase (Lox) as a regulator of astrogliosis

Authors: *A. D. RIVERA, A. BUTT
Univ. of Portsmouth, Portsmouth, United Kingdom

Abstract: Astrocytes are the most numerous glial cells in the brain and perform multiple homeostatic and defence functions that are essential for CNS integrity. Astrocyte ‘reactivity’ or ‘reactive astrogliosis’ is the hallmark of most neuropathologies and is characterised by morphological and functional changes, upregulation of the intermediate filament glial fibrillary acidic protein (GFAP), and often cell proliferation (gliosis). However, astroglial changes in bipolar disorder (BD) are unclear and may be dependent on the brain region and therapeutic regime. Here, we have examined the effects of lithium, the frontline treatment for BD, on astrocytes in the mouse optic nerve, a typical CNS white matter tract. Adult GFAP-EGFP mice were used to identify astrocytes; mice were killed humanely in accordance with the Home Office Animals (Scientific) Act 1986 (UK), and optic nerves isolated with retina intact. Nerves were maintained *ex vivo* in organotypic culture in control medium or medium containing 20 mM lithium chloride. After 3 days *in vitro*, optic nerves were analysed by confocal microscopy, immunohistochemistry, microarray, and qRT-PCR. Lithium had a profound morphogenic and gliotic effect on astrocytes and genomic analysis identified the enzyme lysyl oxidase (LOX) as a key target of lithium in astrocytes. We demonstrate that inhibition of LOX with BAPN markedly altered astrocyte morphology, similar to that observed in lithium. In addition, we establish that Lox is markedly decreased in grey and white matter of occipital cortex from BD patients and this negatively correlates with increased astroglial GFAP expression. The results demonstrate that astrocytes are cellular targets of lithium and identify LOX as a novel negative regulator of astrogliosis, providing a new connection between lithium treatment and potential stabilization of neuronal function and integrity by its actions on astrocytes in BD and other neuropathologies. A.D. Rivera and A.M. Butt report to be shareholders in the company GliaGenesis. *Supported by the BBSRC.*

Disclosures: **A. Butt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gliagenesis Ltd.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.17/I14

Topic: B.11. Glial Mechanisms

Support: Wellcome trust grant to AVG

Title: Purinergic signalling controls bicarbonate secretion in astrocytes to regulate brain extracellular pH

Authors: *S. M. THEPARAMBIL, P. S. HOSFORD, A. V. GOURINE
Dept. of Physiology, Pharmacol. and Neurosci., Univ. Col. London, London, United Kingdom

Abstract: Maintenance of constant extracellular pH environment is fundamentally important to ensure brain function, primarily due to high pH sensitivity of various enzymes as well as neuronal receptors and ion channels involved in synaptic transmission. Astrocytes, the most abundant glial cells of the brain are known to regulate the extracellular concentrations of various ions and metabolites thus playing a critical role in homeostatic control of brain milieu. Astrocytes may also contribute to the regulation of brain extracellular pH and $[\text{HCO}_3^-]$ via the activity of a bicarbonate transporters, in particular electrogenic sodium-bicarbonate cotransporter 1 (NBCe1), which is highly expressed in these cells. NBCe1 in astrocytes transports sodium-bicarbonate with a stoichiometry of $1\text{Na}^+:2\text{HCO}_3^-$, and has an equilibrium potential of ~ -85 mV. Therefore, in steady state, NBCe1 is operating close to its reversal potential in astrocytes. A rise in intracellular $[\text{Na}^+]/[\text{HCO}_3^-]$, a fall in extracellular $[\text{HCO}_3^-]$ or membrane hyperpolarization can stimulate the outward transport of bicarbonate. The activity of NBCe1 is also known to be modulated by intracellular signalling pathways involving Ca^{2+} , IP3R binding protein released with inositol 1,4,5-trisphosphate (IRBIT), cyclic adenosine monophosphate/protein kinase A (cAMP/PKA), and phospholipase C (PLC). In the present study we investigated whether purinergic signalling, mediated by the actions of extracellular purine nucleotides (ATP and ADP), can modulate the NBC-dependent bicarbonate transport in cortical astrocytes. We used wide-field fluorescence microscopy for simultaneous recordings of intracellular pH and $[\text{Ca}^{2+}]$ in cultured astrocytes using pH and Ca^{2+} sensitive dyes, BCECF and X-Rhod-1/Rhod-2, respectively. It was found that application of either ATP or ADP triggers intracellular acidification in bicarbonate-buffered solution, and these responses are markedly reduced by NBC blocker S0859 (100 μM) or anion transport inhibitor DIDS (200 μM). ATP or ADP failed to trigger astroglial pH_i responses in HEPES-buffered solution in the absence of extracellular bicarbonate. ATP induced intracellular acidification and $[\text{Ca}^{2+}]$ responses were abolished in the presence of an ATP receptor antagonist PPADS (100 μM). These results suggest that ATP-mediated purinergic signalling can trigger bicarbonate secretion by astrocytes via enhanced activity of the NBC and contribute to the control of extracellular pH of the brain parenchyma.

Disclosures: S.M. Theparambil: None. P.S. Hosford: None. A.V. Gourine: None.

Poster

042. Astrocyte Biology

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Topic: B.11. Glial Mechanisms

Support: NSERC Discovery Grant 2NS

CFI 2NS

CRC 2NS

Carleton Development Grant

Title: Sex differences in cortical astroglial cells throughout postnatal development in mice

Authors: *G. M. RURAK¹, G. COPPOLA², N. SALMASO¹

¹Neurosci., Carleton Univ., Ottawa, ON, Canada; ²Child Study Ctr., Yale Univ., New Haven, CT

Abstract: Sexual differentiation of the mammalian central nervous system is a robust and well characterized estrogen-dependent phenomena. Fortunately, developmental mechanisms are preserved across species and allows us to employ mice as a model of sexual differentiation in brain development. Sexual dimorphisms of the hypothalamus and some telencephalic regions are well characterized, however sexual dimorphism of the cortex remains contested. The cortex follows well defined stages of development known as cortical neurulation; beginning with radial migration of neuroblasts to the formation of fully functional neuronal networks receiving feedback from the other cortical and subcortical regions. Astroglial cells have emerged recently as vital regulators of the central nervous system by providing trophic, metabolic and structural support to neurons and other glial cells. Interestingly, astroglial cells are functionally relevant at all stages of cortical neurulation; from providing the scaffolding for radial migration of neuroblasts, assisting in the formation and elimination of synapses, promoting myelination, and acting as stem cells under certain circumstances. Despite astroglial cells expressing estrogen receptors, their role in sexual differentiation has been unappreciated. Our present study aims to understand if and when sexual dimorphisms in astroglial cell populations emerge and how they may be functionally relevant to gross sexual dimorphisms found throughout the brain. Using a transgenic mouse line expressing green fluorescent protein (GFP) bound to a ribosomal protein (L10) under the pan-astroglial promoter *Aldh1l1*, we used immunohistochemistry to quantify the total number of astroglial cells (GFP) and those cells expressing glial acidic fibrillary protein (GFAP), vimentin, and *ki67*. We also aimed to characterize the transcriptome of cortical astroglial cells using translating ribosome affinity purification (TRAP) sequencing. Both male and female C57/BL6-GFP-*Aldh1l1*-L10 mice were used at P1, P4, P7, P14, P35 and in adulthood without external manipulation to characterize any baseline sexual dimorphisms in astroglial cell populations. We found significant developmental changes with respect to the number of GFAP+ and vimentin+ astroglial cells; a trend in sexually dimorphic number of vimentin+ astroglial cells in the early postnatal period and in adulthood. Further, work to characterize the sexually dimorphic nature of cortical astroglial cells and their contribution to the development of a sexually dimorphic central nervous system remain to be elucidated.

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

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Program #/Poster #: 042.19/I16

Topic: B.11. Glial Mechanisms

Support: P01HD076892
R01MH099587

Title: Dissecting neuronal contact and activity dependent transcriptional changes in human astrocytes using thiouracil tagging

Authors: ***R. A. BRADLEY**¹, A. PETERSEN³, K. LIU², C. MCFALLS², J. SHIREMAN², S.-C. ZHANG⁴

¹Neurosci., ²Univ. of Wisconsin - Madison, Madison, WI; ³Neurosci., Univ. of Wisconsin Madison, Madison, WI; ⁴Univ. Of Wisconsin Colleges, Madison, WI

Abstract: How neuronal activity regulates astrocytes in a temporal and spatial manner remains largely unknown due to limitations inherent in separating the cells or transcripts for cell type-specific analysis. The use of RNA-tagging technologies can allow for the investigation of cell type-specific transcriptional changes *in situ* without the need for the separation of cells prior to analysis. Thiouracil tagging of nascent RNA in the presence of 4-thiouracil (4TU) and *Toxoplasma gondii* uracil phosphoribosyltransferase (*TgUPRT*) allows for RNA-tagging with both the cell-type and temporal control of labeling, permitting a greater range of applications over previous RNA-tagging technologies. Utilizing co-cultures with neurons expressing designer receptors activated by designer drugs (DREADDs), we identified gene expression changes in astrocytes when the co-cultured neurons are activated or inhibited. This system demonstrates the applicability of using thiouracil tagging in an *in vitro* human PSC-based neuron-astrocyte co-culture model.

Disclosures: **R.A. Bradley:** None. **A. Petersen:** None. **K. Liu:** None. **C. McFalls:** None. **J. Shireman:** None. **S. Zhang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder of BrainXell, Inc..

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.20/I17

Topic: B.11. Glial Mechanisms

Title: Small Ankyrin 1 may regulate SERCA activity in astrocytes but not in neurons

Authors: *A. LABUZA, R. J. BLOCH

Physiol., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Intercellular calcium (Ca^{2+}) regulation is very important for brain function. Ca^{2+} reuptake into the endoplasmic reticulum (ER) is associated with several diseases, including Alzheimer's and Huntington's diseases. Ca^{2+} reuptake into the ER in neurons and astrocytes is mediated by sarco(endo)plasmic reticulum Ca^{2+} -ATPase (SERCA). Our laboratory has recently shown that SERCA activity can be mediated by a small transmembrane protein, small ankyrin 1 (sAnk1), in skeletal muscle.

Here we show that sAnk1 may also regulate SERCA activity in astrocytes but not in neurons.

We have used qPCR and western blot to show sAnk1 and SERCA expression in the CNS.

Immunocytochemistry (ICC) in primary hippocampal cultures (kindly provided by the Blanpied laboratory) showed no localization of sAnk1 and SERCA. This was confirmed by examining single neurons transfected to express gCamp. Neurons filled with gCamp stained for SERCA not for sAnk1. Hippocampal cultures labeled for sAnk1, SERCA, and markers for neurons and astrocytes (NeuN and GFAP respectively) showed sAnk1 expression only in astrocytes.

Therefore, sAnk1 may inhibit SERCA activity in astrocytes, showing a distinct regulation of Ca^{2+} reuptake in astrocytes compared to neurons. These findings will be tested further in studies of isolated primary neurons and astrocytes and by co-immunoprecipitation of sAnk1 and SERCA in astrocytic cultures, compared to neuronal cultures, and by Ca^{2+} -ATPase assays.

Disclosures: A. Labuza: None. R.J. Bloch: None.

Poster

042. Astrocyte Biology

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Program #/Poster #: 042.21/J1

Topic: B.11. Glial Mechanisms

Support: R01AG034389
R01NS095215
NSF1615874

Title: Ceramide-induced interaction between tubulin and voltage-dependent anion channel 1 regulates mitochondria ATP release in astrocytes

Authors: *Z. ZHU¹, A. ELSHERBINI², J.-N. KONG^{3,4}, Y. ITOKAZU⁴, G. WANG², M. DINKINS⁴, L. ZHONG¹, H.-P. LIN¹, S. LEANHART⁴, X. JIANG¹, H. QIN¹, W. ZHI⁴, S. SPASSIEVA², E. BIEBERICH¹

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Abstract: The first two authors contributed equally to this study

Ceramide is a cell signaling sphingolipid known to regulate a plethora of biological functions including cell cycle, apoptosis, and mitochondrial function. Recently, mitochondrial ATP release to the cytosol was shown to depend on the interaction of voltage-dependent anion channel 1 (VDAC1) with tubulin. Using crosslinking to the ceramide analog pacFACer and superresolution fluorescence microscopy, we found that ceramide interacts with tubulin and that ceramide-associated tubulin (CAT) is translocated from the perinuclear region to ceramide-enriched and mitochondria-associated membranes (CEMAMs) that are co-distributed with microtubules. This translocation was prevented in astrocytes deficient of neutral sphingomyelinase 2 (nSMase2), an enzyme generating ceramide from sphingomyelin, or cells treated with Fumonisin B1 (FB1), an inhibitor of ceramide synthases. Proximity ligation and co-immunoprecipitation assays showed that ceramide depletion reduced association of tubulin with VDAC1. Ceramide depletion led to higher levels of ATP in astrocytes, suggesting that ceramide-induced CAT formation leads to VDAC1 closure, thereby reducing mitochondrial ATP release. We also show that mitochondrial motility is increased in nSMase2-deficient astrocytes and that amyloid beta peptide (A β 42) does not induce mitochondrial fragmentation in these cells. These results suggest that CAT regulates mitochondrial motility and that blocking ceramide generation may increase ATP release and protect mitochondria in Alzheimer's disease.

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.22/J2

Topic: B.11. Glial Mechanisms

Support: NIH Grant DA032895

Title: Nuclear and cytosolic compartmentalization of β -adrenergic receptor signaling in astrocytes

Authors: ***D. S. WHEELER**, K. BENTON, B. KURTOGLU, K. COLE, M. CROWE, E. DASSOW, P. WITT, D. C. LOBNER, P. J. GASSER
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Abstract: The conventional model of adrenergic signaling involves activation of plasma membrane receptors, followed by G-protein-mediated signaling within the cytoplasm. However, recent studies have demonstrated that adrenergic receptor signaling can be initiated at intracellular membranes, including the nuclear membrane. Recently, we observed the expression of β 1 adrenergic receptors, and critical G-protein signaling actors in the nuclei of cultured mouse astrocytes. Furthermore, we have demonstrated that organic cation transporter 3 (OCT3), a catecholamine transporter, is localized to the outer nuclear membrane, suggesting that OCT3 allows norepinephrine to access nuclear adrenergic receptors. These observations indicate that nuclear membrane receptors may be an important component of adrenergic signaling in the central nervous system. In a series of experiments, we have sought to determine the function of nuclear and plasma membrane adrenoreceptors. Using nuclear fractionation and western blot analysis, we confirmed the predominant localization of β 1 receptors to the nuclei of astrocytes. Immunofluorescence studies using two different detergents to permeabilize the plasma (digitonin) or plasma and nuclear (triton X-100) membranes to examine the localization PDE4 and PKA revealed the presence of PDE4b and PKA RI in the nuclei of astrocytes. To assess the function of this signaling system, we transfected primary astrocytes with a genetically engineered FRET sensor based upon Exchange Protein Activated by cAMP (Epac) to examine real-time fluctuations in cAMP in response to adrenergic agonists. We observed a robust increase in nuclear cAMP in response to norepinephrine and the β -selective agonist isoproterenol. This signal is blocked by the β -selective antagonist propranolol. Future research will determine whether activation of nuclear adrenergic receptors is gated by outer nuclear membrane catecholamine transporters, and whether blocking uptake could limit nuclear adrenergic activation.

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

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Program #/Poster #: 042.23/J3

Topic: B.11. Glial Mechanisms

Support: Beckman Graduate Fellowship
NSF STC CBET 0939511 (EBICS)
NSF DGE 1735252 (NRT UtB)

Title: Astrocytes in the hippocampal dentate gyrus exhibit diurnal morphological and coupling heterogeneity via label-free imaging

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Abstract: Complex brain functions, including learning and memory, arise in part from the modulatory role of astrocytes on neuronal circuits. We have previously demonstrated a significant diurnal difference in astrocyte organization in key regions of the brain, including the dentate gyrus (DG). Functionally, the DG exhibits differences in acquisition of long term potentiation (LTP) between day and night. We hypothesize that the dynamic nature of these astrocyte networks plays an important role in the functional circuitry of hippocampal learning and memory, specifically in the DG. Standard techniques such as differential interference contrast (DIC) have been unable to correlate astrocyte electrophysiological and coupling properties with the extensive astrocyte branching morphology. Gradient light interference microscopy (GLIM), a quantitative phase imaging label-free technique, allows for imaging of substantially thicker specimens than previously achieved with standard fluorescence-labeling techniques. This enables us to obtain dry mass values of the cell bodies and processes as well as total cell volume measurements that can then be used to quantify the difference in astrocyte branching complexity over the day-night cycle. Our preliminary results found distinct diurnal coupling properties of astrocyte populations within the rat hippocampal DG. Our data suggest that the number of coupled astrocytes is significantly higher during the night than the daytime. These coupled cells display linear voltage-current profiles with very low resistances ($< 20 \text{ M}\Omega$) at both time points. As the number of coupled cells increases, the cellular resistance decreases. We predict a correlation between electrophysiological properties of astrocytic networks and fluctuations of dry mass over the day-night cycle. Utilizing emerging technology of label-free imaging in brain slices along with electrophysiological measurements will allow us to advance our knowledge of the role of astrocytic networks in regulating neuronal circuitry important in learning and memory.

Disclosures: **G. Naseri Kouzehgarani:** None. **M.E. Kandel:** None. **G. Popescu:** None. **M.U. Gillette:** None.

Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

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Program #/Poster #: 042.24/J4

Topic: B.11. Glial Mechanisms

Support: DA031747
DA041513
DA032681

Title: Dopamine effects on astrocyte morphology and transcriptome

Authors: *A. GALLOWAY¹, A. ADELUYI², B. O'DONOVAN¹, M. L. FISHER², M. SAJISH², J. R. TURNER², P. I. ORTINSKI¹

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Abstract: Dopamine is critical for processing of reward and etiology of drug addiction. Astrocytes throughout the brain express dopamine receptors, but consequences of astrocytic dopamine receptor signaling are not well-established. We found that extracellular dopamine triggered rapid concentration-dependent stellation of astrocytic processes that was blunted by inhibition of D1-like and D2-like dopamine receptors, as well as Gq/PLC-linked receptors. Functionally, dopamine reduced duration and increased frequency of astrocytic Ca²⁺ transients. Whole-genome RNA sequencing revealed prominent dopamine-induced enrichment of genes containing the CCCTC-binding factor (CTCF) motif, suggesting involvement of chromatin restructuring. CTCF binding to promoter sites depends on activation of poly-ADP-ribose polymerase 1 (PARP1). Accordingly, antagonism of PARP1 occluded dopamine-induced morphological changes, whereas a PARP1 agonist facilitated morphological changes on its own. Our findings highlight regulation of chromatin landscape as a critical factor in the rapid astrocyte response to dopamine with implications for reward processing and drug addiction.

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Poster

042. Astrocyte Biology

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Topic: B.11. Glial Mechanisms

Support: NIH Grant R01 NS092067
AHA 17POST33670330

Title: Endothelia regulate astrocytic glutamate transporter 1 (GLT-1) expression: A notch story

Authors: *Z. MARTÍNEZ LOZADA, M. L. LEE¹, E. K. SHIH¹, M. B. ROBINSON^{1,2}

¹Children's Hosp. of Philadelphia, Philadelphia, PA; ²Pharmacol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Astrocytes, the most abundant cell type in the central nervous system, are a heterogeneous population with equally diverse functions. Astrocyte roles are favored by their localization, which allows them to contact synapses and enwrap the vasculature. Although the communication between neurons and astrocytes has been broadly studied, the interaction between endothelial cells and astrocytes is less understood. We recently demonstrated that endothelia induce astrocytic expression of the glutamate transporter 1 (GLT-1) by a Notch-dependent mechanism. GLT-1 is responsible for up to 90% of the removal of glutamate from the synaptic cleft in the forebrain and is a marker of astrocyte maturation. For further understanding of the signalling involved in endothelia effect, we use primary cultures of rat astrocytes and the endothelioma cell line bEND.3 or primary rat brain endothelial cells to identify the notch ligand responsible of this effect. We observed that although neutralizing antibodies directed against the Notch ligand Delta like 1 (DLL1) block the effect of endothelia, treatment with recombinant DLL1 is not sufficient to induce astrocytic GLT-1 expression. This in addition to other results suggested that endothelia require the activation of at least two signalling pathways to activate GLT-1 expression in astrocytes. Currently we are evaluating how this signalling is affected by stroke using a photothrombosis model. Understanding the molecular mechanisms involved in endothelia-astrocyte communication is critical to comprehending the biology of this interaction, neurovascular coupling and how this interaction is lost in pathology.

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Poster

042. Astrocyte Biology

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Program #/Poster #: 042.26/J6

Topic: B.11. Glial Mechanisms

Support: AFOSR grant Astronir
AFOSR gran Astromat

Title: Infrared laser photostimulation evokes TRP mediated calcium signaling in primary differentiated rodent astrocytes

Authors: *A. I. BORRACHERO-CONEJO¹, W. R. ADAMS², E. SARACINO³, G. NICCHIA⁴, M. MOLA⁴, F. FORMAGGIO⁵, M. CAPRINI⁵, T. POSATI³, R. ZAMBONI³, M. MUCCINI¹, A. MAHADEVAN-JANSEN², V. BENFENATI³

¹CNR-ISMN, Bologna, Italy; ²Biomed. Engin., Vanderbilt Univ., Nashville, TN; ³ISOF, CNR, Bologna, Italy; ⁴Univ. of Bari, Bari, Italy; ⁵Dept. di Farmacia e Biotecnologie, FABIT, Univ. of Bologna, Bologna, Italy

Abstract: Astrocytes ions and water channels play a key role in brain physiology and pathophysiology. Nonetheless, astroglial Ca²⁺ signaling have been shown to be crucial for astrocytes cell-cell communication as well as in as in neuroglial signaling. In this view, label free tools enabling to investigate/modulate astrocytes protein channels and Ca²⁺ signaling are demanded to unravel biophysical mechanisms underpinning astrocytes physiology. Infrared neural stimulation (INS) has been shown to be an efficient label-free optical method to photostimulate/modulate neuronal firing [1]. Nevertheless, the effect of INS on astrocytes have not been deeply investigated. Here, we explore the effect of INS on intracellular Ca²⁺ dynamics of astrocytes. We found that INS elicits Ca²⁺ signaling in primary rat cultured astrocytes grown on Poly-D-lysine. Interestingly when astrocytes were grown on hydrocalcite, a nanostructured substrate enabling astrocytes differentiation [2], INS elicits Ca²⁺ oscillation in astrocytes cell body and in microdomains. By applying selective pharmacology and siRNA technology, we clearly identify a role for extracellular calcium influx in the response, mediated by TRPV4 and TRPA1 channels. Notably, the response of primary astrocytes from AQP4-KO/- was delayed compared to the one observed in astrocytes from WT animals.

Our results show that thermal response and water influx might underpin the observed effect. Collectively they open the view for the use of INS to modulate astrocytic biophysics at subcellular scale.

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[1] Cayce et al. Cell Calcium. 2014

[2]Posati et al., Sci. Rep. 2016

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Poster

042. Astrocyte Biology

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Program #/Poster #: 042.27/J7

Topic: B.11. Glial Mechanisms

Support: NIH Grant NS096100
NIH Grant MH110724

Title: Cortical astrocytes are derived from two distinct progenitor populations

Authors: *E. C. GINGRICH¹, B. TING¹, P. S. SAKTHIVEL¹, A. D. R. GARCIA^{2,1}
¹Drexel Univ., Philadelphia, PA; ²Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The molecular heterogeneity of astrocytes is gaining widespread recognition, yet little is known about the developmental origins of this diversity. We previously showed that in the adult mammalian cortex, a subpopulation of astrocytes express the transcription factor, Gli1, indicating active and high level Sonic hedgehog (Shh) signaling. Whether Gli1 expression emerges in mature astrocytes or whether the postnatal brain harbors a population of Gli1 progenitor cells is unknown. In this study, we used genetic inducible fate mapping from Gli1CreER mice crossed with the Rosa26 tomato reporter line (*Gli1^{CreER/+};R26^{tdTom/tdTom}*) to examine Gli1 expression during postnatal development. Our data show that the number and distribution of Gli1 cells marked in the early postnatal brain is broader than that observed in the adult. Whereas tamoxifen administration in adult mice marks cells primarily in layers 4 and 5, tamoxifen at P0 exhibit a high density of marked cells in layers 1 and 2/3, suggesting that the early postnatal brain harbors a population of Gli1-expressing progenitors that generate astrocytes with a broad distribution. Tamoxifen at P7 fails to mark cells in the superficial cortex, producing a laminar distribution that is consistent with that observed in the adult cortex. This suggests that astrocytes in the superficial layers downregulate Gli1 expression as they mature, whereas Gli1 expression persists in astrocytes in deep cortical layers. Interestingly, although the vast majority of Gli1-positive cells marked during the first postnatal week produce astrocytes, only half of all mature cortical astrocytes are derived from a Gli1-expressing precursor. This suggests that cortical astrocytes are derived from two progenitor cell lineages. Notably, we also observed a small, but increasing proportion of marked cells that correspond to oligodendrocytes over time, suggesting that the Gli1 progenitor population at P0 harbors a pool of oligodendrocyte precursors. Taken together, these data suggest Gli1-expressing glial progenitors generate two

molecularly distinct astrocyte populations in the mature cortex. Moreover, these data indicate that the diversity observed in cortical astrocytes emerges at the progenitor cell stage during postnatal development.

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

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Program #/Poster #: 042.28/J8

Topic: B.11. Glial Mechanisms

Support: NIH R01 NS086933-01
Alzheimer's Association MNIRGDP-12-258900

Title: Role of AKT isoforms in reactive astrogliosis

Authors: *R. A. MILSTEAD, J. LEVENGA, H. WONG, C. HOEFFER
Univ. of Colorado, Boulder, Boulder, CO

Abstract: **ABSTRACT** Reactive astrogliosis is a stimulus-dependent process that is heavily involved in neurological insults and neurodegenerative disease. Recently, reactive astrogliosis has been categorized into two subtypes. One form of reactive astrogliosis can be induced by infectious and inflammatory insults, such as lipopolysaccharide (LPS) injection. As a result of LPS insults, neurodegenerative reactive astrocytes are induced, and these are known as A1 astrocytes. Another form of reactive astrogliosis can be induced by ischemic and cytotoxic insults, including strokes and seizures. Following ischemia, neuroprotective reactive astrocytes, also known as A2 astrocytes, are produced. Although the levels of gene expression in A1 and A2 astrocytes have been extensively studied, the mechanism that determines the fate of reactive astrocytes is largely unknown. AKT is a central protein kinase involved in many of the cellular signaling pathways implicated in A1 and A2 reactive astrocytes. There are three structurally similar AKT isoforms (AKT1/PKB α , AKT2/PKB β , AKT3/PKB γ). In mouse models deficient in each individual isoform, certain differences in behavior and physiology are apparent. Recent data from our group shows that AKT2 is selectively expressed in astrocytes. To understand the role of AKT2 in astrocytes, we are investigating *Akt* mutant mice and pharmacological treatments combined with biochemical and histological analyses of different astrogliosis models. Given that AKT2 seems to be selectively expressed in astrocytes and could be involved in both A1 and A2 reactive astrogliosis, AKT2 may be a promising target for future therapies aimed at astrocyte activity.

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

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Program #/Poster #: 042.29/J9

Topic: B.11. Glial Mechanisms

Support: NCCR synapsy
NCCR Transcure

Title: Vmat2 in astrocytes regulates dopamine homeostasis in the developing prefrontal cortex

Authors: *T. ZEHNDER¹, F. PETRELLI¹, L. PUCCI¹, G. DALLÉRAC², C. CALÌ¹, S. SULTAN¹, C. ASENSIO³, V. GUNDERSEN⁴, N. TONI¹, G. KNOTT⁵, F. MAGARA⁶, F. KIRCHHOFF⁷, N. DÉGLON⁸, B. GIROS⁹, R. EDWARDS³, J.-. MOTHET², P. BEZZI¹

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Abstract: Astrocytes can influence many aspects of synaptic transmission, network activity, and cognitive functions by controlling the extracellular homeostasis of ions and neurotransmitters. However, whether and how astrocytes participate in regulating the homeostasis of dopamine (DA) has never been investigated in detail. Recent advances indicate that astrocytes express proteins involved in DA uptake and metabolism such as mitochondrial monoamine oxidase B (MAOB) enzyme [Zhang et al., *Neuron*, 2016] and, importantly, vesicular monoamine transporter 2 (VMAT2) [Romero-Calderon et al., *Plos Gen*, 2008; Zhang et al., *Neuron*, 2016], an integral vesicular membrane protein that directly controls vesicular storage of monoamines in neurons and neurosecretory cells [Edwards et al., *Neuron*, 2007]. Here, we find that a subset of cortical astrocytes is crucial in maintaining an efficient DA homeostasis in the developing prefrontal cortex (PFC) through expression of VMAT2. Astrocytes start to express VMAT2 during the early stage of postnatal development preceding adolescence, i.e. when the establishment of DA connectivity in the PFC occurs. At subcellular level VMAT2 in astrocytes is responsible for sequestering DA in intracellular organelles and, thus, for regulating the amount

of cytosolic DA available for metabolism through MAOB activity. By using *in vivo* conditional gene inactivation and viral-mediated gene replacement we find that extracellular levels of DA in the developing PFC can be controlled through modulation of VMAT2 expression in astrocytes. Interestingly, we also show that dysfunction of VMAT2-dependent homeostatic control of DA by astrocytes alters an efficient acquisition of behavioral and cognitive performances. *Support contributed: NCCR Synapsy and NCCR TransCure to P. Bezzi*

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Poster

042. Astrocyte Biology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 042.30/J10

Topic: B.11. Glial Mechanisms

Support: WMU Internal Funds

Title: Adult zebrafish astroglial response to olfactory organ damage in the olfactory bulb

Authors: ***J. SCHEIB**, C. BYRD-JACOBS
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Abstract: Glial cells can be activated in response to injury and disease. In the mammalian CNS, astrocytes proliferate in response to CNS insults and, in severe cases, will form a permanent glial scar that limits neuroplasticity. This is due to two distinct subclasses of reactive astrocytes: hypertrophic and scar-forming. Zebrafish are a reliable model for neuroplasticity studies, but the glial role in plasticity is relatively unexplored in this model system. Zebrafish do not have mammalian-type astrocytes, but they possess glial fibrillary acidic protein- (GFAP-) positive cells with processes similar to mammalian glia. Investigating the zebrafish astroglial role in olfactory system neuroplasticity may lead to a better understanding of neurological disorders where reactive gliosis causes secondary damage.

We used the zebrafish olfactory system to study reactive astroglia in response to peripheral damage. Our hypothesis is that insults to the zebrafish olfactory organ will cause astroglia in the olfactory bulb to react similarly to mammalian astrocytes, with proliferation and hypertrophy. The olfactory organ was damaged using a wax plug inserted into the right nasal cavity every twelve hours for varying time points, while the left organ was kept untreated as an internal control. Astroglial processes in the olfactory bulb were identified using antibodies for GFAP. In

control bulbs, anti-GFAP revealed sparse, fibrous profiles in the internal cell layer, more staining in the glomerular layer, and predominant labeling in the olfactory nerve layer. Unlike the radial glial labeling in the telencephalon, the labeled profiles in the olfactory bulb did not appear organized: there was no clear cell body and the fibers ran in all directions. At 1d, 3d, and 7d of wax plug insertions, we observed an apparent increase in GFAP labeling throughout the affected bulb compared to control bulbs. This increase in glia is coincident with olfactory sensory neuron axonal degeneration. Three weeks of cessation of wax plug insertion allowed the olfactory organ to recover, axons reinnervated the glomerular layer, and the bulb showed a return to control levels of anti-GFAP labeling. These findings suggest a hypertrophy response similar to the reactive astrocytes in the mammalian CNS, but further studies are needed to examine whether scar formation occurs. These glial populations might be a key to understanding the dynamic neuroplasticity of zebrafish.

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Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

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Program #/Poster #: 043.01/J11

Topic: B.11. Glial Mechanisms

Support: McGill University Integrated Program in Neuroscience Returning Student Award (ZC)
MNI–Cambridge Douglas Arvith Award (ZC)
National Sciences and Engineering Research Council Canada Graduate Scholarship (ZC)
MNI–Cambridge Collaborative Grant (ER).

Title: Myelination in the developing *Xenopus laevis*

Authors: *Z. CHORGHAY¹, E. S. RUTHAZER²

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Abstract: Myelination of axons by oligodendrocytes (OLs) increases the efficiency of information transmission in the central nervous system. The African claw-toed frog, *Xenopus laevis*, is a good model for the study of neurodevelopment, due to its amenability for electrophysiology, in vivo imaging, and targeted genetic and pharmacological manipulations of externally developing embryos. Previous studies have reported the initial appearance of OLs, at stage (st) 42 in the hindbrain (Yoshida, 1997) and after stage st 48 in the optic nerve (Cima and Grant, 1982). However, a comprehensive characterisation of the timecourse of myelin ensheathment in *Xenopus* has been lacking. Here, we used the localisation of myelin basic

protein (MBP) as a proxy for myelin ensheathment, since MBP is a late OL marker, is abundantly present in myelin, and is highly conserved across species (Harauz et al., 2004). We collected a detailed developmental time series for MBP immunofluorescence at various tadpole stages. We conclude that the overall pattern of initial myelin ensheathment during neurodevelopment in *Xenopus* occurs similarly to that of other species, with MBP staining first occurring in the hindbrain and spinal cord, then in the cranial nerves beginning from the brain and myelinating outwards to the periphery, and finally, in the communicating fibers within the brain itself.

Disclosures: **Z. Chorghay:** None. **E.S. Ruthazer:** None.

Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 043.02/J12

Topic: B.11. Glial Mechanisms

Support: Danish medical research council

Title: KIF21B regulates myelination in zebrafish

Authors: **J. STEENGAARD**¹, **K. KJAER-SORENSEN**¹, ***L. S. LAURSEN**²

¹Dept. of Mol. Biol. and Genet., ²Aarhus Univ., Aarhus, Denmark

Abstract: Myelination is a complex biological process requiring spatial migration and timely differentiation of individual oligodendrocytes to wrap its membrane around nearby axons. Correct microtubule organization followed by actin polymerization and depolymerization at the growth cone like structure of the individual oligodendrocyte processes are key events in the myelination process. The intracellular factors involved in coordinating process extension and retraction, however, remains to be fully understood. Kinesin motor proteins act in microtubule dynamics and transports cargos along microtubules in both non- and polarized cells. The function of kinesin motor proteins have been extensively studied in neurons, but eventhough several kinesin motors are known to be expressed in oligodendrocytes, only a few have been studied. The kinesin 4 family member KIF21B have been linked to a higher susceptibility of developing multiple sclerosis via single nucleotide polymorphism (SNP) in an intron and downstream of the *kif21b* gene. The functional role of KIF21B in neurons is reported to include both interfering with microtubule dynamics as well as cargo transport. Interestingly, KIF21B knockout in mice also resulted in changes within corpus callosum, one of the major white matter tracks; however it is unclear whether these changes are caused by myelination abnormalities. In this study, we aim to determine whether changes in KIF21B expression may result in myelination abnormalities and as such be an underlying cause of disease development in

multiple sclerosis. Initially, we used transgenic zebrafish expressing a fluorescent reporter in mature oligodendrocytes, as a model system. Following morpholino mediated knockdown of KIF21B, in this system, two major phenotypes were observed. Firstly, the zebrafish larvae displayed a marked delay in their escape response, and secondly we observed a significant reduction in mature oligodendrocytes expressing the fluorescent reporter. A more detailed analysis of KIF21B function in primary oligodendrocytes, revealed that KIF21B is highly enriched in the growth cone like structures of the precursor cells. siRNA mediated knock down and over expression of KIF21B further supported that KIF21B is important at different steps during early differentiation of the oligodendrocyte precursors.

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Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

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Program #/Poster #: 043.03/J13

Topic: B.11. Glial Mechanisms

Support: NIH Grant NS082203

Title: PAK1 regulation of oligodendrocyte differentiation and myelination

Authors: T. L. BROWN, L. T. FINSETH, *W. B. MACKLIN
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Abstract: Oligodendrocytes, the myelinating cells of the central nervous system (CNS), undergo myriad morphological and cytoskeletal changes during differentiation and myelination. Myelin ensheaths axons to increase speed of action potential conduction while providing metabolic and trophic support to neurons. Increases in oligodendrocyte density and myelination are associated with learning complex motor tasks, while disruption of myelin causes serious motor and sensory dysfunction in diseases such as multiple sclerosis. Despite significant advances in understanding oligodendrocytes and their role in the CNS, much remains unknown about the molecular control of oligodendrocyte development and myelination. During development, actin assembly regulates oligodendrocyte process extension and initial axon ensheathment, while actin disassembly promotes myelin wrapping. It is unclear what regulates these changes in cytoskeletal dynamics throughout oligodendrocyte differentiation. One potential mechanism of cytoskeletal regulation is through p21-activated-kinase (PAK1), a serine/threonine kinase that regulates both the Akt pathway and the actin cytoskeleton. The scaffolding function of PAK1 is required for activation of the Akt pathway, one of the major signaling pathways regulating oligodendrocyte development, while the PAK1 kinase activity regulates actin turnover. Pak1 is expressed throughout the oligodendrocyte lineage but its role throughout OPC differentiation and

myelination has not been extensively studied. Using zebrafish to investigate the mechanism by which PAK1 may regulate oligodendrocyte differentiation, we have pharmacologically inhibited the kinase domain of PAK1. Inhibiting the kinase activity of PAK1 decreased oligodendrocyte morphological differentiation, myelin gene expression and myelin internode length. Overexpression of dominant negative PAK1 in zebrafish oligodendrocytes decreased internode length, while constitutively activating PAK1 increased myelin internode length. These *in vivo* studies support a model in which PAK1 regulates the amount of myelin produced by individual oligodendrocytes. Further research is required to determine the role of PAK1 in the Akt/mTOR pathway and the mechanism by which PAK1 regulates oligodendrocyte differentiation and myelination.

Disclosures: T.L. Brown: None. L.T. Finseth: None. W.B. Macklin: None.

Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 043.04/J14

Topic: B.11. Glial Mechanisms

Support: Swedish Research Council
ERC Consolidator Grant EPISCOPE
Swedish Brain Foundation
Ming Wai Lau Centre for Reparative Medicine
Petrus och Augusta Hedlunds Foundation
Karolinska Institutet

Title: Oligodendrocyte lineage subtypes equally originate from embryonic and postnatal waves and have spatial preference in the mammalian central nervous system

Authors: *E. M. FLORIDDIA, S. ZHANG, J. P. GONÇALVES DOS SANTOS, G. CASTELO-BRANCO
Karolinska Institutet, Stockholm, Sweden

Abstract: Oligodendrocytes (OLs) are the myelinating cells of the central nervous system. OLs insulate and metabolically support axons, resulting in optimal motor, sensory, and higher-cognitive functions. The OL lineage is formed of twelve transcriptionally distinct subtypes detected by single-cell RNA-seq. The functional consequences of the OL transcriptional heterogeneity are unknown.

Here, we investigated the spatial distribution of the OL subtypes to gain insight on their potential circuitry preference. We observed a homogenous distribution of the progenitor stages (OPCs and committed OPCs) in both the juvenile and adult brain and spinal cord.

Two of the mature OL subtypes (MOL2 and MOL5/6) show spatial preference. MOL2 preferentially distribute in the white matter of the spinal cord at the level of the dorsal column and are almost absent in the cortex and corpus callosum. While MOL5/6 are most abundant in the corpus callosum in the brain and in the dorsal horn of the spinal cord. When we focused our analysis on the dorsal funiculi, we observed that MOL5/6 preferentially distribute at the level of the dorsal corticospinal tract. Remarkably, dorsal column tracts and corticospinal tracts transmit proprioceptive signals to the brain and motor control to the periphery, respectively. These long-projecting tracts conduct electric impulses at different speeds, suggesting MOL2- and MOL5/6-specific myelin properties.

Furthermore, we investigated whether the OPC fate towards specific OL subpopulations is predetermined by their developmental origin. We fate mapped OPCs at embryonic day 13.5 (first wave of origin) and postnatal days 3 to 5 (last wave of origin) taking advantage of the $Pdgfra::CreER^{T1}$ -GFP mouse model and analyzed the maturation of OPCs in juvenile and adulthood. We did not observe any influence of the OPCs developmental origin on their differentiation potential.

Altogether, our data show that the developmental origin does not influence the OPC fate and mature OL subpopulations have spatial preference. These data suggest potential effects on the myelinating properties of the OL subpopulations and modulation of neuronal function. Further understanding of the functional properties of the OL subpopulations will impact how we modulate remyelination in disease.

Disclosures: E.M. Floriddia: None. S. Zhang: None. J.P. Gonçalves dos Santos: None. G. Castelo-Branco: None.

Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 043.05/K1

Topic: B.11. Glial Mechanisms

Title: Understanding the molecular mechanisms underlying differential myelination in the cortex

Authors: *V. A. JOKHI, P. ARLOTTA

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Abstract: Myelination of axons represents a unique milestone in vertebrate brain evolution, which has enabled the expansion of the brain and complex brain function. Until recently, it was assumed that myelin was distributed uniformly along all axons, however, we have shown that distinct mammalian neurons are endowed with different profiles of myelin distribution, including the notable examples of neurons in layer 2/3 of cerebral cortex, which are responsible for higher-order functions yet present “intermittent” myelination with large of portions of their axons being

surprisingly “naked” (Tomassy et al., Science, 2015). The work provides a new conceptual framework to evaluate the roles of myelin for circuit functionality and suggest the possibility that different neurons may use different strategies for long distance communication. Using molecular profiling, high-resolution imaging and a pilot screen we investigate how diverse populations of neurons and oligodendrocytes interact to achieve neuron type-specific programs of myelination.

Disclosures: V.A. Jokhi: None. P. Arlotta: None.

Poster

043. Oligodendrocyte Development and Function

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Program #/Poster #: 043.06/K2

Topic: B.11. Glial Mechanisms

Support: Stem Cells Australia (Australian Research Council))
ARC FT150100207 (TDM)

Title: Regeneration of NG2 glia following pharmacogenetic ablation in the adult central nervous system

Authors: *T. D. MERSON¹, B. H. A. CHUANG², T. J. KILPATRICK³, S. MITEW², Y. L. XING²

¹Merson Group, Australian Regenerative Med. Inst., Monash University, Australia; ²Australian Regenerative Med. Inst., Monash Univ., Clayton, Australia; ³The Univ. of Melbourne, Parkville, Australia

Abstract: NG2-glia have been investigated principally in terms of their function as oligodendrocyte progenitor cells (OPCs) in the central nervous system (CNS). Additional roles of NG2-glia in adult brain physiology, particularly the modulation of neural processing, have been suggested, but the underlying mechanisms remain elusive. Attempts to investigate the function of NG2-glia by targeted cell ablation in the adult CNS have been limited by methodological challenges resulting in only partial and transient OPC ablation. To overcome these limitations we have developed a novel transgenic mouse model of conditional NG2-glia ablation. Crossing *Pdgfra-CreER^{T2}* mice with a Cre-dependent *Sox10-DTA* mouse line, enabled the ablation of the vast majority of *Pdgfra⁺/NG2⁺* cells in a tamoxifen-dependent manner. We found that residual non-ablated NG2-glia rapidly proliferated to repopulate the CNS. However, when tamoxifen administration was followed by the intracisternal infusion of the antimetabolic drug cytosine- β -D-arabinofuranoside (AraC), we observed complete ablation of NG2-glia throughout the brain for 10 days. Strikingly, from this time-point onwards, *Pdgfra⁺/NG2⁺* cells gradually reappeared and progressively repopulated the brain. Combined genetic fate-mapping and pharmacogenetic ablation of NG2-glia using *Pdgfra-CreER^{T2}::Sox10-DTA::Rosa-LSL-tdTomato* mice revealed

that almost none of the newly-generated Pdgfra⁺/NG2⁺ cells derived from non-ablated NG2-glia. In contrast, we found that new Pdgfra⁺/NG2⁺ cells arose first in regions adjacent to the subventricular zone (SVZ) and progressively migrated throughout the brain. These data are consistent with the possibility that the ablation of NG2-glia in the normal adult brain mobilises a population of oligodendrogenic neural precursor cells (NPCs) from the SVZ that exhibit extensive migratory potential. Our data support the notion that adult NPCs have the capacity to migrate extensively throughout the CNS and that strategies targeted towards mobilising NPCs could promote remyelination of demyelinated lesions located large distances from the SVZ.

Disclosures: T.D. Merson: None. B.H.A. Chuang: None. T.J. Kilpatrick: None. S. Mitew: None. Y.L. Xing: None.

Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

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Program #/Poster #: 043.07/K3

Topic: B.11. Glial Mechanisms

Support: ZIAHD000713-22
DoD11162432

Title: Regulation of myelin structure and conduction velocity by perinodal astrocytes

Authors: D. J. DUTTA, D. WOO, P. R. LEE, S. PAJEVIC, O. BUKALO, H. WAKE, *W. HUFFMAN, P. J. BASSER, S. SHEIKHBAHAEI, V. LAZAREVIC, J. C. SMITH, R. D. FIELDS
NIH, Bethesda, MD

Abstract: The proper speed of impulse transmission is critical for optimal neural circuit function, but it is unclear how the appropriate conduction velocity is established and maintained in individual axons. In vertebrate axons, the velocity of impulse transmission is influenced by the thickness of the myelin sheath and the morphology of electrogenic nodes of Ranvier along axons. Here we show that myelin thickness and nodal gap length are reversibly altered by astrocytes, glial cells that contact the nodes of Ranvier. Thrombin-dependent proteolysis of a cell adhesion molecule that attaches myelin to the axon (Neurofascin 155), is reduced by vesicular release of thrombin protease inhibitor from perinodal astrocytes. Transgene-induced reduction in exocytosis from astrocytes in-vivo resulted in detachment of adjacent paranodal loops of myelin from the axon, increasing nodal gap length and thinning the myelin sheath. These morphological changes alter the passive cable properties of myelinated axons to reduce conduction velocity, and electrophysiological recordings in optic nerve and visual cortex of mice show that conduction velocity and spike time arrival in the CNS were reduced in parallel with a decrease in visual

acuity. All effects were reversed by the thrombin inhibitor Fondaparinux. Prior to these findings, it was unknown how the myelin sheath could be thinned and the functions of astrocytes in myelinated tracts were not well understood. These findings contribute a new form of nervous system remodeling in which myelin structure and conduction velocity are adjusted by astrocytes. The thrombin-dependent cleavage of Neurofascin 155 may also have relevance to demyelinating disorders.

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Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 043.08/K4

Topic: B.11. Glial Mechanisms

Title: Neuronal activity promotes the adaptive myelination of oligodendrocytes from human pluripotent stem cells *in vitro*

Authors: ***T. BRICKLER**, J. BIAN, J. VEGA LEONEL, S. CHETTY
Stanford Univ., Stanford, CA

Abstract: Oligodendrocytes (OLs) are a type of glial cell that generate and produce myelin around axons in the central nervous system (CNS). OLs play a critical supportive role during normal development and throughout adulthood in maintaining proper conductance of electrical signals produced by neurons and regulating neuron stability and survival. Defects in myelin formation and maintenance can lead to the onset and progression of neurodegenerative diseases such as multiple sclerosis and may underlie a host of other neurological illnesses such as neuropsychiatric disorders. The generation of oligodendrocytes from human pluripotent stem cells (hPSCs) is a powerful tool for studying the development of oligodendrocytes and elucidating the cellular mechanisms underlying myelination. However, current protocols typically rely on embryoid body formation followed by inefficient and long stepwise processes spanning 3-4 months that yield OLs with limited or no capacity for myelination *in vitro*. Here, we develop a defined stepwise protocol for generating expandable oligodendrocyte progenitor cells from hPSCs that mature and myelinate neurons *in vitro* within a few weeks. The *in vitro* derived oligodendrocytes express markers of the oligodendroglial lineage, including Olig2, Olig1, Nkx2.2, Sox10, O4, PDGFR α , and MBP, and suppress genes associated with the neuronal and astrocytic lineages. Importantly, we show that neuron conductance promotes myelination of those axons and neurons that do not have strong electrical conductance remain un-myelinated. This co-culture system is mutually beneficial in enhancing the maturation of OLs and neurons.

Using this new protocol, we demonstrate the utility of the *in vitro* derived oligodendrocytes for disease modeling and cell replacement therapy in neurodegenerative disorders.

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Poster

043. Oligodendrocyte Development and Function

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Program #/Poster #: 043.09/K5

Topic: B.11. Glial Mechanisms

Support: NIDA IRP
NSF Grant 1232825

Title: Oligodendrocytes contribute to brain glutamate homeostasis

Authors: *W. XIN^{1,2}, Y. MIRONOVA¹, H. SHEN², R. MARINO², A. WAISMAN³, W. LAMERS⁴, D. E. BERGLES¹, A. BONCI^{2,1}

¹Neurosci., Johns Hopkins Univ., Baltimore, MD; ²Synaptic Plasticity Section, Natl. Inst. on Drug Abuse, Baltimore, MD; ³Inst. for Mol. Med., Univ. Med. Ctr. of the Johannes Gutenberg-University Mainz, Mainz, Germany; ⁴Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Glutamate is the major excitatory neurotransmitter in the brain. Glutamate uptake and degradation are critical for neuronal signaling and prevention of excitotoxicity, and perturbations of these processes accompany numerous pathological states, including epilepsy, stroke, and ALS. Currently, glutamate uptake and degradation within the brain are thought to occur exclusively in astrocytes - ubiquitous glial cells that express glutamate transporters as well as the glutamate metabolizing enzyme glutamine synthetase (GS). However, a handful of studies have also reported GS expression by oligodendrocytes. Oligodendrocytes produce myelin and ensheath axons to provide electrical insulation, but they have largely been ignored in the context of glutamate regulation. Therefore, we set out to confirm the expression of GS by oligodendrocytes and determine whether they functionally contribute to glutamate processing. qPCR and fluorescent in situ hybridization revealed high levels of GS mRNA in oligodendrocytes, and immunostaining with validated GS antibodies confirmed expression at the protein level. Although they do not express glutamate transporters, approximately 90% of oligodendrocytes are structurally coupled to astrocytes via gap junctions and thus may access extracellular glutamate through astrocytic uptake. Most strikingly, animals in which GS was specifically deleted from oligodendrocytes had significant decreases in tissue levels of glutamate and glutamine, as well as a reduction in the size of electrically evoked glutamate currents onto midbrain neurons. These results represent a profound departure from the canonical view of glutamate metabolism in the brain and identify a novel, myelin-independent role for

oligodendrocytes. As such, oligodendrocytes may represent a new target for treatment in diseases that involve glutamate dysregulation.

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Poster

043. Oligodendrocyte Development and Function

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Program #/Poster #: 043.10/K6

Topic: B.11. Glial Mechanisms

Support: HHMI Gilliam Fellowship
Medical Research Foundation pilot award

Title: Oligodendrocyte specific transcriptional profiling: From candidate genes to in-vivo functional assays

Authors: *A. FOSTER¹, B. EMERY²

¹Neurol., Oregon Hlth. and Sciene Univ., Portland, OR; ²Jungers Ctr. for Neurosciences Res., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Oligodendrocytes are central nervous system glial cells that ensheath neuronal axons allowing for rapid and energy-efficient propagation of electrical signals. Oligodendrocytes are derived from the oligodendrocyte progenitor cells (OPCs), which continuously give rise to new myelinating oligodendrocytes both during development and into adulthood. Previous studies have used transcriptional profiling at distinct stages of the oligodendrocyte to identify key genes regulating myelination, however these studies have typically been limited to development as current techniques to isolate oligodendrocyte specific RNA such as immunopanning or fluorescence-activated cell sorting (FACS) become progressively more difficult with age, limiting their utility in adult rodents. Alternative strategies such as RNA-TRAP can be more readily used in the adult, but only capture actively translating mRNA, which cannot be used to study total mRNA or non-coding RNA. In order to address this void, we have used the INTACT (isolation of nuclei tagged in specific cell types) nuclear purification method to isolate highly pure RNA samples from OPCs and OLs in the adult mouse brain. RNA-Seq comparative analysis identifies clear differentiation induced RNA expression profiles between adult OPC populations compared to actively myelinating oligodendrocytes. In addition, we have developed an AAV-based *in-vivo* CRISPR screening system that allows for selective disruption of genes in the oligodendrocyte lineage and assessment of their effects on differentiation and myelination. Together, these techniques will help identify molecular mechanism regulating oligodendrocyte function not only throughout development but also into adulthood and in disease models.

Disclosures: **A. Foster:** None. **B. Emery:** A. Employment/Salary (full or part-time); Oregon Health and Science University.

Poster

043. Oligodendrocyte Development and Function

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Program #/Poster #: 043.11/K7

Topic: B.11. Glial Mechanisms

Support: NIH NS082203
NMSS RG5371-A-4

Title: Mechanistic target of rapamycin regulates the oligodendrocyte cytoskeleton during myelination

Authors: ***T. L. WOOD**¹, A. S. MUSAH¹, T. L. BROWN², H. HASHIMOTO², W. B. MACKLIN²

¹Dept Pharmacology, Physiol. & Neurosci., New Jersey Med. Sch, Rutgers Univ., Newark, NJ;

²Cell and Developmental Biol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: During differentiation, oligodendrocyte precursor cells (OPCs) extend a network of processes that make contact with axons and initiate myelination. Recent studies revealed that actin polymerization is required for initiation of myelination whereas actin depolymerization promotes myelin wrapping. However, it is unknown how these pathways orchestrate the morphological changes observed during differentiation and myelination. Studies in other cell types demonstrate a clear role for the mechanistic target of rapamycin (mTOR) pathway in regulating the cytoskeleton and our previous studies revealed that mTOR regulates oligodendrocyte differentiation and developmental myelination and is necessary for normal myelin thickness in the spinal cord (Tyler et al., 2009; Wahl et al., 2014). Collectively, these findings led us to hypothesize that mTOR regulates cytoskeletal dynamics in oligodendrocytes necessary for initiation of myelination and for proper myelin wrapping.

To test our hypothesis, we pharmacologically inhibited mTOR with rapamycin during oligodendrocyte differentiation in primary rat OPC cultures and in zebrafish and analyzed a mouse line with oligodendroglia-specific deletion of mTOR during developmental myelination. We demonstrate that loss or inhibition of mTOR reduces expression of profilin2 and ArpC3, actin polymerizing factors, and elevates levels of active cofilin, that mediates actin depolymerization. The deficits in actin polymerization are revealed in a reduction in oligodendrocyte branching at the peak of morphological differentiation and a delay in initiation of myelination. We further show a critical role for mTOR in expression and localization of myelin basic protein that is necessary at the myelin membrane for actin depolymerization during axon wrapping. These data support the conclusion that mTOR regulates both initiation of

myelination and axon wrapping by targeting cytoskeletal reorganization.

Tyler WA, Gangoli N, Gokina P, Kim HA, Covey M, Levison SW, Wood TL (2009) Activation of the mammalian target of rapamycin (mTOR) is essential for oligodendrocyte differentiation. *J Neurosci* 29:6367-6378.

Wahl SE, McLane LE, Bercury KK, Macklin WB, Wood TL (2014) Mammalian target of rapamycin promotes oligodendrocyte differentiation, initiation and extent of CNS myelination. *J Neurosci* 34:4453-4465.

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Poster

043. Oligodendrocyte Development and Function

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Topic: B.11. Glial Mechanisms

Support: NIH Fellowship T32 HD7249

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Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Mbp mRNA transport in oligodendrocytes is critical for myelin maintenance

Authors: *M.-M. FU, C.-Y. LEE, B. BARRES

Neurobio., Stanford Univ., Stanford, CA

Abstract: Efficient electrical signaling along neuronal axons depends on the formation of compact myelin. Myelin compaction is a bizarre cellular phenomenon that relies on myelin basic protein (MBP), which acts as a molecular zipper to exclude cytoplasmic proteins and organelles from regions of compact myelin. By RNA-Seq, *Mbp* is the most highly expressed mRNA in oligodendrocytes by over 10-fold. It is also a special protein whose mRNA must be transported along oligodendrocyte processes by the microtubule motor kinesin before it is distally translated. Here, we further elucidate the mechanisms of *Mbp* mRNA transport by performing a non-biased proteomic screen in cultured oligodendrocytes using the RNA-binding reporter protein MS2. We identify many novel hits, including putative signaling proteins and adaptor proteins that link mRNAs to motors. We characterize two of these hits - the retrograde microtubule motor dynein and the actin motor myosin. Surprisingly, impaired dynein activity impedes anterograde *Mbp* mRNA transport, indicating a bidirectional mechanism of transport that relies on both kinesin and dynein. A zebrafish mutant in dynactin, a key adaptor for dynein, displays myelination

defects. When myosin activity is blocked, *Mbp* mRNA is no longer distributed on actin. Mutations in this myosin are found in human patients with distal myopathy that can present with white matter lesions. Blocking either dynein or myosin activity results in abrogated MBP protein translation. Finally, we test the in vivo implications of blocking *Mbp* mRNA transport by generating a mouse that lacks *Mbp* 3'UTR. Whereas the classic shiverer mouse that cannot express MBP exhibits tremors at 2 weeks of age, *Mbp* 3'UTR knockout mice only begin to exhibit tremors at 2-3 months. This result surprisingly indicates that *Mbp* mRNA transport is crucial in the adult animal and perhaps occurs in adult oligodendrocytes along cytoplasmic channels that penetrate through layers of myelin. In order to understand this, we are currently employing cell culture, histology and electron microscopy approaches. Together, these experiments indicate that complex interactions between motor proteins coordinate the efficient delivery of *Mbp* mRNA, which is crucial for myelin maintenance in adult mice.

Disclosures: M. Fu: None. C. Lee: None. B. Barres: None.

Poster

043. Oligodendrocyte Development and Function

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Program #/Poster #: 043.13/K9

Topic: B.11. Glial Mechanisms

Support: NIH NS094151
NIH NS105689
NMSS RG5239-A-3

Title: The UPR is required for maintaining ER protein homeostasis and the viability and function of adult mature oligodendrocytes

Authors: *W. LIN¹, S. STONE², S. WU²

¹Neurosci., Univ. of Minnesota Dept. of Neurosci., Minneapolis, MN; ²Univ. of Minnesota, Minneapolis, MN

Abstract: Oligodendrocytes must produce enormous amounts of myelin proteins to assemble myelin sheath or to maintain myelin structure homeostasis. Myelin proteins are synthesized, modified, and folded in the endoplasmic reticulum (ER). Maintaining ER protein homeostasis is essential and necessary for the myelinating function of oligodendrocytes. Nevertheless, the mechanisms by which oligodendrocytes maintain ER protein homeostasis remain unknown. The unfolded protein response (UPR), which comprises three parallel signaling pathways IRE1, PERK, and ATF6 α , is the principle ER quality control mechanism that maintains ER protein homeostasis by facilitating protein folding, attenuating protein translation, and enhancing protein degradation. It has been demonstrated that deletion of either PERK or ATF6 α does not affect

oligodendrocytes under normal conditions. Intriguingly, we found that double deletion of PERK and ATF6 α in oligodendrocytes did not affect developmental myelination, but led to late-onset tremoring phenotype, oligodendrocyte death, and demyelination in adult mice. Moreover, we found that double deletion of PERK and ATF6 α induced soma retention of proteolipid protein (PLP, accounting for ~ 50% of total myelin proteins in the CNS) in oligodendrocytes. A number of studies have shown that overexpression of PLP leads to soma retention of PLP in oligodendrocytes, resulting in adult-onset dysmyelination in the CNS. Thus, these data suggest that the UPR maintains ER protein homeostasis and the viability and function of adult mature oligodendrocytes by enhancing degradation of PLP.

Disclosures: W. Lin: None. S. Stone: None. S. Wu: None.

Poster

043. Oligodendrocyte Development and Function

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Topic: B.11. Glial Mechanisms

Support: MOST 106-2314-B-006 -041 -MY3

Title: Interleukin-33 signaling is involved in glial progenitor cell Proliferation and oligodendrocyte differentiation

Authors: H. HUANG¹, H.-Y. SUNG², C.-H. HO¹, C.-Y. WANG¹, W.-Y. CHEN⁴, *S.-F. TZENG³

¹Natl. Cheng Kung Univ., Tainan, Taiwan; ²Life Sci., Natl. Cheng Kung Univ., Tainan city, Taiwan; ³Natl. Cheng Kung Univ., Tainan City, Taiwan; ⁴Inst. for Translational Res. in Biomedicine, Chang Gung Mem. Hosp., Kaohsiung, Taiwan

Abstract: Interleukin-33 (IL33) is a member of IL1 family and derived from pro-IL33 and acts as an extracellular cytokine. Mature IL-33 functions as an “alarmin” to induce T helper 2 (Th2) immune responses in immune cells via interaction with its receptor ST2 and IL-1 receptor accessory protein. The pro-IL-33 protein contains a nuclear localization sequence (NLS), an N-terminal homeodomain-like helix-turn-helix (HTH) motif, and a chromatin-binding domain. Although the pro-IL33 can translocate from the cytoplasm into the nucleus, the function of the nuclear IL-33 in the cells remains unclear. Previously, we have demonstrated that IL-33 regulates the proliferation of rat and human glioma cells possibly through IL-33/ST2 axis. In addition, our recent study has found that IL-33 was enriched in the nuclear fractions of rat and human glioma cells, and associated with the chromatin fibers. The nuclear IL-33 was also detected in oligodendrocyte precursor cells (OPCs). The results from IL-33 immunostaining indicated that IL-33 was mainly expressed in the cells of the CNS white matter. Further

observations showed that IL-33 gene knockdown in OPCs can suppress the differentiation of OPCs into oligodendrocytes (OLGs). Through in vivo study by the examination of the animal behaviors, IL33 knockout (KO) mice displayed the higher frequency of the center entry in the open field with a longer duration when compared to those observed in the control group. In an elevated plus maze test, IL33 KO mice stayed longer in the open arms. The results suggest that the absence of IL33 function caused animals with a tendency toward a fearless behavior. While the mechanism underlying IL33 regulation of OLG differentiation, the present findings provide important information that IL-33 is required for OLG maturation and the regulation of animal behavior.

Disclosures: **H. Huang:** None. **H. Sung:** None. **C. Ho:** None. **C. Wang:** None. **W. Chen:** None. **S. Tzeng:** None.

Poster

043. Oligodendrocyte Development and Function

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Topic: B.11. Glial Mechanisms

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NIH Grant NS080619
Loglio Initiative
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Title: Endocytosis pathway control of proteoglycan NG2 is linked to oligodendrocyte progenitor asymmetric division and differentiation

Authors: ***C. K. PETRITSCH**, M. CHOUCANE

Dept. of Neurolog. Surgery, Univ. of California San Francisco, San Francisco, CA

Abstract: A fraction of oligodendrocyte progenitor divides asymmetrically generating one proliferating OPC and one differentiating oligodendrocyte. One of the earliest changes in the differentiating progeny is the loss of the pro-mitotic NG2 proteoglycan expression. Whether NG2 is downregulated by transcriptional or post-translational mechanisms is unclear, and thus asymmetric cell division and oligodendrocyte differentiation mechanisms are not fully understood. Here, we provide evidence that endocytic trafficking controls the surface levels of NG2 by a mechanism that requires cell polarity regulator Lethal giant larvae 1. Lgl1 conditional knockout cKO oligodendrocytes retain NG2 expression and show differentiation defects. They undergo more symmetric self-renewing divisions at the expense of asymmetric divisions in the

healthy and demyelinated murine brain. Moreover, Lgl1 and hemizygous Ink4a/Arf knockout synergistically induce gliomagenesis. Time-lapse and total internal reflection microscopy reveals a critical role for Lgl1 in NG2 endocytic routing and link aberrant NG2 protein recycling to failed differentiation and asymmetric division. Data from ongoing single cell analyses of OPC progeny of asymmetric and symmetric divisions are expected to provide novel mechanistic insights into early differentiation and will be presented at the meeting.

Disclosures: C.K. Petritsch: None. M. Chouchane: None.

Poster

043. Oligodendrocyte Development and Function

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Topic: B.11. Glial Mechanisms

Support: A Grant-in-Aid for Scientific Research (C) of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) in Japan

Title: Teneurin-4 regulates oligodendrocyte process formation in CNS myelination

Authors: *N. SUZUKI^{1,2}, Y. YAMADA²

¹TMDU/Department of Mol. and Cell. Biol., Tokyo, Japan; ²NIDCR, NIH, Bethesda, MD

Abstract: In the CNS, oligodendrocytes form myelin, which insulate neuronal axons and enable the rapid propagation of action potential. Defects in CNS myelination cause various types of neuronal and mental disorders. However, the detailed molecular mechanisms of oligodendrocyte development and CNS myelination have not been fully understood. In this study, we identified a mouse mutation caused by a transgene insertion that resulted in tremors and hypomyelination in the CNS, particularly in the spinal cord. In the mutant mice, myelination of small diameter axons and the number of oligodendrocytes were dramatically reduced. We subsequently identified the transgene insertion site into the teneurin-4 (Ten-4) gene encoding a transmembrane protein, whose function was unknown. We found that Ten-4 was highly expressed in the spinal cord of wild-type mice and was induced during normal oligodendrocyte differentiation. In the mutant mice, however, the expression of Ten-4 was absent, indicating that the deficiency of Ten-4 expression was responsible for the CNS defects. Primary oligodendrocytes from the mutant mice failed to form well-branched cellular processes in culture. In the oligodendrocyte progenitor cell line CG-4, suppression of Ten-4 expression by shRNA inhibited process formation. Moreover, the deficiency of Ten-4 attenuated the activation of the focal adhesion kinase in vivo and in vitro. These findings indicate that Ten-4 is a key regulator of oligodendrocyte process formation and is required for CNS myelination. This mutant mouse model will facilitate a better understanding of

oligodendrocyte biology, as well as of the development of diagnostic and therapeutic reagents for dysmyelinating diseases.

Disclosures: N. Suzuki: None. Y. Yamada: None.

Poster

043. Oligodendrocyte Development and Function

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 043.17/K13

Topic: B.11. Glial Mechanisms

Support: A Grant-in-Aid for Scientific Research (C) of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) in Japan

Title: Oligodendrocyte-axon interaction via teneurin-4 controls cell adhesion in morphogenesis of oligodendrocytes for myelination

Authors: *C. HAYASHI, N. SUZUKI, N. KIKURA, Y. HOSODA, Y. MABUCHI, C. AKAZAWA

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Abstract: Oligodendrocytes (OLs), myelinating cells in the central nervous system (CNS), facilitate the rapid propagation of action potential and the formation of neural precise networks. The interaction of OLs with axons is essential for myelination, and its abnormality causes mental and neural diseases. Our previous study revealed that Teneurin-4 (Ten-4), a type II transmembrane protein, was a key regulator of myelination in the CNS. Ten-4 was expressed on oligodendrocyte precursor cells (OPCs)/OLs, and depletion of Ten-4 caused hypomyelination in the small diameter axons. Furthermore, Ten-4 deficient mice developed tremors. However, molecular mechanisms of Ten-4 function in myelination have not been well understood. Here we show that crucial roles of Ten-4 on OPCs/OLs in myelination. Myelin formation is a complex sequence of events and OL-axon interaction is important for several steps during myelination. Initial steps of myelination are 1) adherence of OPCs/OLs to targeted axons, 2) process extension of OLs with actin assembly in leading edges of the processes, and 3) ensheathment of axons by the extended OL processes. Our *in vivo* analysis demonstrated that defects in adherence and process extension were observed in Ten-4 deficient mice. Furthermore, these mice displayed the reduction of actin assembly in the cytoplasm of myelin. From the above, Ten-4 was required for the initial steps of myelination. Hence, we next explored the binding partners of Ten-4 for the OL-axon interaction, and as a result, Ten isoforms (Ten-1, Ten-2, Ten-3, and Ten-4) were selected as candidates. First, we assessed the cell-cell adhesion activity between Ten-4 and Ten isoforms and found that Ten-4-overexpressing cells formed larger cell aggregates with all Ten isoforms-overexpressing cells homophilically and heterophilically. In addition, OPCs/OLs

attached to the recombinant extracellular domains of Ten-1 to -4 (rTen-1ECD, rTen-2ECD, rTen-3ECD, and rTen-4ECD), and especially rTen-1, -3, and -4ECD showed high attachment activity of OPCs/OLs. The attachment activity was inhibited in the presence of soluble rTen-4ECD. Therefore, we proposed that Ten-4 on OPCs/OLs presumably interacted with Ten isoforms on axons. Finally, to examine the effect of binding of Ten-4 with Ten isoforms, we cultured OPCs/OLs on rTen-1 to -4ECD and found promoted OL process formation with actin assembly. These results revealed that Ten-4 plays a crucial role in cell adhesion and cytoskeletal organization in oligodendrocytes for CNS myelination.

Disclosures: C. Hayashi: None. N. Suzuki: None. N. Kikura: None. Y. Hosoda: None. Y. Mabuchi: None. C. Akazawa: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.01/K14

Topic: C.01. Brain Wellness and Aging

Support: 2R01AG033649-07

Title: Long-term intranasal aspart in the aged F344 model of aging: From pathway analysis to behavior, and insulin receptors to mechanisms of brain insulin resistance

Authors: *K. L. ANDERSON¹, H. N. FRAZIER¹, A. O. GHOWERI¹, K. VATTANAPHONE², M.-F. XIA², G. A. FOX⁴, E. SUDKAMP², E. S. JOHNSON¹, K. E. HARGIS¹, J. C. GANT¹, L. D. BREWER¹, N. M. PORTER¹, J. R. PAULY³, E. M. BLALOCK¹, O. THIBAUT¹
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Abstract: Intranasal (IN) insulin has been tested in clinical and pre-clinical settings as a potential therapeutic to combat decreased insulin signaling in the brain of Alzheimer's disease (AD) patients. The approach has demonstrated improved memory in young volunteers and in patients with mild cognitive impairment. Similarly, in animal models of aging, diabetes, or AD, the impact of IN insulin has provided evidence for improved cognitive function. We and others have previously reported that acute or short term IN delivery of different insulin formulations can enhance insulin signaling in the brain, alter cerebral blood flow, and enhance memory recall. Here, we tested whether long term IN insulin provided greater enhancement in memory and recall in young and aged rats, and whether continued presence of the ligand might cause receptor downregulation.

We characterized the impact of long term (3 months, > 60 doses) IN insulin aspart (NovoLog®) on behavior using the Morris water maze (MWM) as well as on insulin receptor (IR) levels using

autoradiography and immunohistochemistry. We also investigated the effect of long term daily doses of insulin on hippocampal RNA species using microarray analyses. Saline (0.9%) or insulin aspart (equivalent to 10 IU/day; 10uL total/day) delivery was accomplished on non-anesthetized animals (n=10-13 per group) as previously published by our group. Young and aged rats showed differences in learning and memory, consistent with previous studies. Use of IN insulin provides evidence of improved MWM performance in the aged animals during the memory test. IHC data show changes in hippocampal IR levels that decrease with age and decrease further with IN insulin. Autoradiographic analysis of [125I] Insulin binding showed no reductions with age but did show a trend towards decreased expression in the olfactory bulb in response to long term IN insulin delivery, albeit only in young animals. Other areas analyzed include hippocampus, cortex and prefrontal cortex. After quality control and pre-statistical filtering, transcriptional profiles (Clariom_S-Rat arrays, N = 26) for hippocampal RNA were analyzed using two way ANOVA ($p \leq 0.01$; False Discovery Rate = 0.24). Overall, aging had the most powerful effect on the transcriptome (70% of all significant genes). Although there was no evidence of a strong effect of insulin selectively in aged brain, IN insulin was associated with a significant downregulation of Ca²⁺ signaling pathways as well as insulin-related genes. Together, these results provide new insights into insulin's mechanism of action in the brain, and provide a greater understanding of insulin resistance in the brain of the young and aged.

Disclosures: H.N. Frazier: None. A.O. Ghoweri: None. K. Vattanaphone: None. M. Xia: None. G.A. Fox: None. E. Sudkamp: None. E.S. Johnson: None. K.E. Hargis: None. J.C. Gant: None. L.D. Brewer: None. N.M. Porter: None. J.R. Pauly: None. E.M. Blalock: None. O. Thibault: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.02/K15

Topic: C.01. Brain Wellness and Aging

Support: NIH 2R01AG033649-07
NIH T32-DK007778

Title: Inducing elevated insulin receptor signaling via a constitutively active human insulin receptor leads to alterations in glucose metabolism in cultured hippocampal neurons

Authors: *H. N. FRAZIER¹, K. L. ANDERSON¹, A. O. GHOWERI¹, S. D. KRANER², G. J. POPA³, M. D. MENDENHALL³, C. M. NORRIS², O. THIBAUT¹

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Abstract: Recent studies indicate that insulin signaling diminishes with aging as evidenced by decreased signaling markers, reduced insulin mRNA, and lower insulin receptor (IR) density. Current evidence highlights the role of insulin in normal brain function, with early stage clinical trials reporting a positive impact of intranasal insulin on memory recall in patients with mild cognitive decline or Alzheimer's disease (AD). Yet, the mechanisms behind this effect remain unclear. To address this, we conducted a series of experiments exploring the relationship between insulin signaling, cellular metabolism, and calcium homeostasis in neurons and astrocytes by using a molecular approach to constitutively increase insulin signaling, thus bypassing the need for exogenous insulin delivery.

Mixed, primary hippocampal cultures were infected with plasmids encoding a red fluorescent protein (mCherry), with or without a truncated, constitutively active form of the human insulin receptor (IR β), using a lentiviral system. To address cell selectivity, a synapsin or GFAP promoter was included to limit expression to either neurons or astrocytes, respectively. Immunocytochemistry against HA-tagged IR β was used to confirm IR β expression. Western immunoblots measuring pAkt/Akt ratio were performed to obtain IR signaling levels. To assess the effect of increased IR signaling on glucose metabolism, 2-NBDG imaging experiments were performed. Glucose uptake was obtained by measuring initial 2-NBDG fluorescence. Fluorescent signal decay over time was recorded as an indirect measure of glucose utilization (Pancani et al., 2011). To test if changes in glucose were related to GLUT4 receptor density, immunocytochemistry using GLUT4 antibody was performed. To more thoroughly characterize associations between glucose, calcium, and IR signaling, calcium imaging using Fura-2 was also conducted.

Lentiviral infection was successful for all constructs. Immunocytochemistry showed the presence of IR β in 80% of cells. Western blots provided evidence that IR β expression confers elevated IR signaling compared to controls. 2-NBDG imaging indicated IR β expression was associated with increased glucose uptake and utilization in hippocampal neurons. Expression of IR β correlated with changes in GLUT4 density. Results were corroborated by evidence of changes in ATP production and intracellular calcium levels.

This characterization provides insights into potential mechanisms governing insulin's effect on memory and learning, and highlights the validity of exploring molecular approaches to enhance insulin signaling to combat cognitive decline associated with AD and aging.

Disclosures: H.N. Frazier: None. K.L. Anderson: None. A.O. Ghoweri: None. S.D. Kraner: None. G.J. Popa: None. M.D. Mendenhall: None. C.M. Norris: None. O. Thibault: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.03/K16

Topic: C.01. Brain Wellness and Aging

Support: FSU-I-03/14
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FP 7/HEALTH.2011.2.2.2-2 GA No.:279281
FKZ 16SV7209
DFG FOR 1738 B2

Title: Tissue-specific gene expression changes are associated with aging in mice

Authors: *A. SRIVASTAVA¹, E. BARTH^{2,3}, M. A. ERMOLAEVA³, C. FRAHM¹, M. MARZ^{2,3}, O. W. WITTE¹

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Abstract: Motivation: Aging is a complex process that can be characterized by functional and cognitive decline in an individual. Aging can be assessed based on the functional capacity of vital organs and their intricate interactions with one other. Thus, the nature of aging can be described by focusing on a specific organ and an individual itself. However, to fully understand the complexity of aging one must investigate not only single tissues or biological processes but also their complex interplay and interdependencies.

Results: Using RNA-Seq, we have monitored changes in the transcriptome during aging in multiple tissues in mice at 9 months, 15 months and 24 months, with a final evaluation at the very old age of 30 months. We could identify several genes and processes that are differentially regulated in aging in both tissue-dependent and tissue-independent manners. Most importantly, we found the electron transport chain of mitochondria to be similarly affected on the transcriptome level in multiple tissues during the aging process. We also identified the liver as the tissue that shows the largest variety of differential expressions over time. We conclude from our study that the molecular processes of aging are relatively subtle in their progress, and the aging process of every tissue depends on the tissue's specialized function and environment. Hence, single genes or processes alone cannot be described as the key of aging in the whole organism.

Disclosures: **A. Srivastava:** A. Employment/Salary (full or part-time):: Full, Jena University Hospital, Hans-Berger Department of Neurology, Jena. **E. Barth:** None. **M.A. Ermolaeva:** None. **C. Frahm:** None. **M. Marz:** None. **O.W. Witte:** None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.04/K17

Topic: C.01. Brain Wellness and Aging

Support: RO1 AGO51807

Title: The age-associated stressors amyloid beta oligomers and oxidative damage induce repressive histone methylation in cultured hippocampal neurons

Authors: *A. IONESCU¹, L. TONG¹, K. TSEUNG², N. BERCHTOLD¹, C. W. COTMAN¹
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Abstract: Age is the number one risk factor for cognitive decline, and recent findings show that epigenetics play a role in regulating age-related changes in learning and memory. Our lab has previously found that a specific repressive epigenetic mark, histone 3 lysine 9 trimethylation (H3K9me3) is increased in the hippocampi of aged mice and patients with Alzheimer's disease. Selective repression of H3K9me3's catalyzing enzyme, SUV39H1, in aged mice increased hippocampal BDNF levels, hippocampal spine density and cognition as measured by behavioral tasks. This pilot study investigated if stressors related to aging, including amyloid beta oligomers and oxidative stress, could induce an increase in H3K9me3 levels in an *in vitro* model. Rat hippocampal neurons were cultured to 7 or 12 DIV prior to treatment with amyloid beta oligomers or 3 amino triazole (3AT), a reliable inducer of oxidative damage. Results suggest that treatment with sub-lethal concentrations of amyloid beta oligomers or 3AT significantly increase levels of H3K9me3 in cultured rat hippocampal neurons. This supports previous findings that H3K9me3 increases in the hippocampus with age and Alzheimer's disease, and is suggestive of a stress-dependent mechanism for H3K9me3 expression.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.05/K18

Topic: C.01. Brain Wellness and Aging

Support: CNPq Grant No. 476634/2013-01

Title: Extracellular vesicles profile is altered in cerebrospinal fluid of aged rats

Authors: *I. R. SIQUEIRA¹, G. ANDRADE³, K. BERTOLDI¹, F. GALVÃO, Jr.⁴, P. WORM⁵, L. R. CECHINEL²

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⁴PPG Fisiologia, Universidade Federal do Rio Grande do Sul, PORTO ALEGRE, Brazil; ⁵Dept. de Neurocirurgia, Complexo Hospitalar Santa Casa de Misericórdia, Porto Alegre, Brazil

Abstract: Our purpose was to study exosomal markers and inflammatory cargo of extracellular vesicles obtained from cerebrospinal fluid (CSF) in aging process. The Local Ethics Committee (CEUA - Comissão de Ética no Uso de Animais - UFRGS; nr.29818) approved all animal procedures and experimental conditions. It was used male Wistar rats of 3-month-old and 21-month-old. Rats were anesthetized with a mixture of ketamine and xylazine (respectively, 75 and 10 mg/kg). The isolation of extracellular vesicles was performed using a commercial kit (ExoQuick™ System Bioscience). CD63 and IL-1 β levels, total protein concentration, acetylcholinesterase (AChE) activity were determined. CSF obtained from aged adult rats showed lower total protein concentration, in addition to higher CD63 content and AChE activity in extracellular vesicles compared to young adult ones. IL-1 β levels were unaltered in CSF extracellular vesicles of aged animals. Our data suggest that the healthy aging can modify the central extracellular vesicle profile.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.06/DP04/L1

Topic: C.01. Brain Wellness and Aging

Support: CIHR grant MOP-102723
Alzheimer Society of Canada grant 17-04
Ontario Graduate Scholarship

Title: Retrograde axonal transport of BDNF diminishes with age in basal forebrain cholinergic neurons

Authors: **A. SHEKARI**, *M. FAHNESTOCK
McMaster Univ., Hamilton, ON, Canada

Abstract: Profound and early basal forebrain cholinergic neuron (BFCN) degeneration is a hallmark of Alzheimer's disease. BFCNs depend for their survival and function on neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) which are retrogradely transported from BFCN target tissues. In Alzheimer's disease, NGF-immunoreactive material is found at abnormally high levels in BFCN targets like cortex and hippocampus and is reduced in basal forebrain, implicating dysfunctional retrograde axonal transport of

neurotrophins in the disease. Age is the greatest risk factor for developing Alzheimer's disease, yet the influence of age on BFCN axonal transport is poorly understood. To model aging, embryonic day 18 rat basal forebrain or cortical neurons were cultured in microfluidic chambers for four weeks. DIV7 neurons were classified as “young” and DIV21 neurons as “aged”, confirmed by staining for senescence-associated beta-galactosidase, a well-validated marker of aging. Biotinylated BDNF was conjugated to quantum dots and added to the axonal compartment of the chambers. Transport data was analyzed using NIH ImageJ. Significant reductions in BDNF transport speed were seen in aged BFCNs but not in aged cortical neurons. Increases in BDNF pause duration were also observed solely in aged BFCNs. Furthermore, mitochondrial axonal transport was dramatically reduced in aged BFCNs compared to young neurons. These results strongly suggest an inherent vulnerability of BFCNs to age-induced retrograde axonal transport deficits. BFCNs’ unique susceptibility to age-induced retrograde axonal transport impairments, coupled with their reliance on neurotrophin transport for proper function, may explain their vulnerability to age-related disorders like Alzheimer's disease.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.07/L2

Topic: C.01. Brain Wellness and Aging

Support: KAKENHI 17K07073

KAKENHI 22500305

Japan Science and Technology Agency (JST) Core Research for Evolutional Science and Technology (CREST)

Title: A novel bdnf subtype bdnf pro-peptide and tau pathology

Authors: *M. KOJIMA¹, K. MATSUI², T. MIZUI³

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Abstract: The microtubule-associated protein tau is a principal component of neurofibrillary tangles, and a key molecule in Alzheimer’s disease and other tauopathies. Although the pathogenic role of tau has been studied extensively, the causal connection between synaptic dysfunction and tau pathology is not fully understood.

Recently, we identified a new subtype of BDNF (brain-derived neurotrophic factor) namely BDNF pro-peptide. It is produced together with BDNF by proteolytic processing of precursor BDNF. Interestingly, however, while BDNF elicited long-term potentiation (LTP) and promoted dendritic spines, the BDNF pro-peptide facilitated long-term depression (LTD) and exerted spine

shrinkage (Mizui et al., PNAS, 2015, 2017), suggesting that the BDNF pro-peptide is a new facilitator of synaptic depression and synapse loss.

In the present study, we investigated how the protein levels of BDNF, its receptor TrkB, BDNF pro-peptide and its receptor component p75 changed in the mouse brain with age. Very interestingly, while a synaptic facilitator BDNF significantly declined the levels with age, the pro-peptide and its receptor p75 pronouncedly raised with age, showing that the biological action of BDNF and its pro-peptide are attenuated and enhanced, respectively, during aging. More interestingly, we found that, in line with the increased amount of the BDNF pro-peptide and p75, tau protein was hyperphosphorylated with age, raising a new possibility that the BDNF pro-peptide/p75 signaling elicits the progression of the tau-hyperphosphorylation-dependent Alzheimer disease and other tauopathies.

Disclosures: M. Kojima: None. K. Matsui: None. T. Mizui: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.08/L3

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant R37-AG004542

Title: Glucocorticoid receptor density increases with aging in rat hippocampal CA1 neurons, showing an inverse relationship to FK506 binding protein 12.6/1b, a major Ca²⁺ regulator

Authors: *I. KADISH¹, J. C. GANT², E. M. BLALOCK⁵, K.-C. CHEN³, O. THIBAUT⁶, N. M. PORTER⁴, P. W. LANDFIELD⁴

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Abstract: A longstanding hypothesis proposes that glucocorticoids (GCs) accelerate and exacerbate deleterious brain aging processes (Porter & Landfield, 1998). Substantial evidence supports this hypothesis but there are also considerable contradictory findings. The conflicting results may in part reflect the fact that GCs are among the most pleiotropic and widely-acting hormones, functioning primarily by binding and activating the glucocorticoid receptor (GR), a nuclear transcription factor. GRs are highly expressed in brain and are particularly enriched in some regions of the hippocampal formation. Another confounding aspect is that multiple genomic targets of the GR exhibit gain of function (GOF) during aging whereas many others

exhibit loss of function (LOF) with aging (Chen et al, 2013). Furthermore, it is not clear which targets and pathways may mediate GC/GR effects on aging.

One candidate pathway for mediating GC effects on brain aging is [Ca²⁺] dysregulation in hippocampal CA1 neurons, an alteration consistently associated with brain aging (Disterhoft & Oh, 2007; Thibault et al, 2007). [Ca²⁺] dysregulation is exacerbated by GCs (Kerr et al, 1989; Joels & deKloet, 1989). Recently, we have found that an aging-related decline in expression of a Ca²⁺ regulator, FK506 binding protein 12.6/1b (FKBP1b) may account for much of the aging-related [Ca²⁺] dysregulation in CA1 (Gant et al, 2015). Here, we test whether an age-related increase in GR expression is associated with the decline of FKBP1b expression. Using immunohistochemical staining of both the GR and FKBP1b in male F344 rats of 5 ages, we find a clear aging-related rise in GR expression concomitant with the decrease in FKBP1b expression, particularly in CA1 cells. Accordingly, our results support the hypothesis that a rise during aging in GR expression in CA1 cells plays a key role in aging-related decline of FKBP1b and increased [Ca²⁺] dysregulation.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: JSPS-Kakenhi 5515K14352

Tacked science foundation 20320625

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Title: Transcriptome analysis by CAGE-seq in the young and old cultured neurons

Authors: *K. MURAI, G. MATSUMOTO, M. FUCHINO, N. MORI

Dept. of Anat. and Neurobio., Nagasaki-University Sch. of Med., Nagasaki, Japan

Abstract: Aging is a major risk for various neurodegenerative conditions including Alzheimer's and Parkinson's diseases, but it is not clear yet what kinds of changes could be the major risk of the aged neurons leading to such pathological conditions of neurodegeneration. Limited activities of proteasomes and/or autophagy could be a primary cause for the accumulation of protein aggregates including A β and tau, but other cellular features such as oxidative stress response and damage repair could also be crucial for maintaining neuronal cellular activities in the aged brain. During the past decades, several studies pointed out that various sets of genes were affected in their expression in the brain of young and old mice and rats. However, it is still

unclear whether there are critical genes and/or signaling processes leading the aging signature of neurons. We developed a long-term culture system of the primary cortical neurons derived from mouse embryonic brains, of which neurons could be survived at least for the maximum 6 month. In those long-term cultured neurons, we performed whole transcriptome analysis using Cap analysis of gene expression (CAGE), to assess the aging signature of neurons. We compared the whole transcriptome between the young (1 month-old) and old (4 month-old) neurons. Gene ontology analysis of the differentially expressed genes showed that genes involved in 'inflammatory response' and 'response to oxidative stress' were enriched in upregulated genes in the 4-months cultured neurons, whereas the nuclear-related genes involving in 'nucleosome organization' and/or 'DNA-protein complex' were enriched in downregulated genes in the old neurons. In addition, pathway analysis implicated that change of gene expression pattern in long-term cultured old neurons were associated, in part, with insulin and insulin-like growth factor signaling pathways. Further features of aging-related transcriptomic changes of the long cultured neurons will be discussed. *This work is supported in part by JSPS-Kakenhi.*

Disclosures: K. Murai: None. G. Matsumoto: None. M. Fuchino: None. N. Mori: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.10/L5

Topic: C.01. Brain Wellness and Aging

Support: U01 MH106882
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T32 GM008136-30

Title: CNV neurons are rare in aged human neocortex

Authors: *W. D. CHRONISTER¹, M. B. WIERMAN¹, I. E. BURBULIS¹, M. J. WOLPERT¹, M. F. HAAKENS¹, J. E. KLEINMAN², T. HYDE², D. R. WEINBERGER², S. BEKIRANOV¹, M. J. MCCONNELL¹

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Abstract: Megabase-scale somatic copy number variants (CNVs) alter allelic diversity in a subset of human neocortical neurons. Reported frequencies of CNV neurons range from ~5% of neurons in some individuals to greater than 30% in other individuals. Genome-wide and familial studies implicitly assume a constant brain genome when assessing the genetic risk architecture of neurological disease, thus it is critical to determine whether divergent reports of CNV neuron

frequency reflect normal individual variation or technical differences between approaches. We generated a new dataset of over 800 human neurons from 5 neurotypical individuals and developed a computational approach that measures single cell library quality based on Bayesian Information Criterion and identifies integer-like variant segments from population-level statistics. A brain CNV atlas was assembled using our new dataset and published data from 10 additional neurotypical individuals. This atlas reveals that the frequency of neocortical CNV neurons varies widely among individuals, but that this variability is not readily accounted for by tissue quality or CNV detection approach. Rather, the age of the individual is anti-correlated with CNV neuron frequency. Fewer CNV neurons are observed in aged individuals than young individuals.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: NIA/NIH Grant 1K99AG055683-01
NIA/NIH Grant 2AG01971911A1

Title: Disrupting the epigenome in novel NICE mice to study age-related cognitive decline

Authors: *J. M. ROSS^{1,2}, G. COPPOTELLI¹, J. AMORIM^{1,3}, E. HILLSTEDT^{1,2}, E. NEEDHAM¹, E. POTTS¹, D. A. SINCLAIR¹

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Abstract: Aging of the brain is a cause of cognitive decline and the major risk factor for neurodegenerative diseases, such as Alzheimer's disease. Epigenetic noise has been highly implicated in both aging *per se* and cognitive impairment. In order to delineate the role of epigenetics in age-related cognitive decline, we are investigating two novel models that allow for precise control and tissue specificity in inducing non-mutagenic, site-specific double-strand DNA breaks by using the homing endonuclease I-PpoI. The ICE mouse has whole-body inducible changes in the epigenome, whereas the NICE mouse has neuronal-specific inducible changes in the epigenome. Barnes maze results demonstrate that 15 month-old ICE mice underperformed with regards to memory recall, compared to age-matched Cre controls. Additionally,

while ICE mice were able to learn the paradigm similarly well as controls, they employed unusual learning strategies. In the elevated plus maze, ICE mice spent more time in and actively sought out the open arms suggesting a decrease in thigmotaxis. Although no major impairments in spatial working memory were detected with the Y-maze, open-field testing showed an increase in time spent in the center of the arena. The NICE mouse has successfully been generated, with offspring viable and healthy. Western blot and immunohistochemistry analyses confirm induction of *I-PpoI* expression and DNA damage in key brain regions, including cerebral cortex, hippocampus, and striatum, but not in peripheral tissues. Additionally, preliminary data show expression of inflammatory markers in hippocampus from NICE mice. Ongoing studies aim to elucidate how DNA damage and chromatin remodeling can elicit neuronal functional changes, which may identify treatment strategies for age-related diseases and disorders of the brain.

Disclosures: **J.M. Ross:** None. **G. Coppotelli:** None. **J. Amorim:** None. **E. Hillstedt:** None. **E. Needham:** None. **E. Potts:** None. **D.A. Sinclair:** None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.12/L7

Topic: C.01. Brain Wellness and Aging

Support: R01 MH109466

Title: The effects of tacedinaline (histone deacetylase inhibitor) on antipsychotic drug induced side effects in aged mice

Authors: ***B. M. MCCLARTY**¹, L. RUOXU¹, G. RODRIGUEZ¹, H. DONG²

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Abstract: Antipsychotic drugs are commonly prescribed to treat the wide range of behavioral and psychological symptoms of dementia (BPSD), which over 90% of AD patients have. However, the severe side effects and increased mortality by antipsychotics in aged patients are a great concern for clinical treatment of BPSD. Currently, there is no efficient treatment available for BPSD in AD, therefore in order to develop new treatment strategies, we must understand the underlying mechanisms of BPSD. Previously, we have found that histone modifications at antipsychotic drug target receptors during aging play a role that affect the actions of drugs. Specifically, we have shown increased repressive histone markers at gene promoters such as dopamine receptor 2 (*Drd2*) and serotonin receptor 2A (*5HT-2A*) leading to decreased receptor expression and functionality in aged mice. In this study, we continue this line of the work to test

whether specific histone deacetylase inhibitors (HDACis) can reverse aging induced hypoacetylation at specific lysine residues and reduce motor and memory side effects caused by antipsychotic drugs. We tested HDACi Tacedinaline (CI994), a selective class 1 HDACi at dose 10 mg/kg and 50 mg/kg for chronic treatment alone or combined with haloperidol (0.05 mg/kg) in aged (19-21 months) and young (2-3 months) C57 mice for same treatment as control. Then a series of behavioral tests for locomotion and memory function and biochemical analysis for histone markers expression and function were measured. Our results show a general motor decline and impairments of recognition memory in aged mice treated with haloperidol alone. When administering CI994 alone, our behavioral assays show an increase of motor and memory performance in aged mice. However, when co-administering CI994 and haloperidol in aged mice, a trend to increase in motor and memory performance was observed, but not significantly compared to aged mice receiving haloperidol alone. For our biochemical analysis, we have found significant increases in histone lysine markers (H₃K18ac and H₃K27ac) in the striatum of aged mice, suggesting CI994 can rescue histone acetylation in the striatum. Now we are testing if CI994 could reduce the HAL induced motor and memory side effects by regulation of histone modifications at the *Drd2* gene promoter in aged mice. Next, we will test if acetylation levels can be rescued globally in cortex and hippocampal tissue of aged mice. We also will test if such effects of CI994 display a dosage response of 50 mg/kg of CI994 administration. This study will further advance our understanding of a novel mechanism by which age-related histone modifications alter antipsychotic drug action.

Disclosures: B.M. McClarty: None. L. Ruoxu: None. G. Rodriguez: None. H. Dong: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.13/L8

Topic: C.01. Brain Wellness and Aging

Title: Neuroprotection and anti-aging effects of anthocyanidins via histone acetylation regulation

Authors: *T. NATORI, T. SUNOHARA, M. MIYAJIMA
Univ. Yamanashigakuin, Yamanashi, Japan

Abstract: Histone deacetylase (HDAC), which regulates gene expression by removing histone acetyl group, is known to be deeply involved in cellular senescence, neurodegenerative diseases and cancer. Resveratrol known as an activator of HDAC regulates the expression of various genes via histone deacetylation. On the other hand, sodium butyrate and valproic acid known as inhibitors of HDAC regulate the expression of various genes by promoting histone acetylation. In addition to the effect of improving nerve function and protective effect, these HDAC modulating agents have also been reported to have a prolonged life span. Recently, it has been

reported that polyphenols have a function of regulating HDAC activity, and the neuroprotective effect and anti - aging effect of these molecules may be epigenetic regulation. Therefore, we examined whether the anti-aging or neuroprotective effect of anthocyanins which is one of polyphenols, is epigenetic mechanism.

We examined the HDAC inhibitory activity of anthocyanins using fluorescent substrate peptides. Cyanidin, delphinidin, peonidin and petunidin significantly inhibited HDAC activity. Therefore, we examined the neuroprotective effect of anthocyanins using human brain-derived neuroblastoma type (SH-SY5Y cell line), and as a result, significant neuroprotective effect was confirmed for cyanidin and peonidin. Furthermore, we investigated the neurite outgrowth promoting effect using neurons derived from mouse embryonic brain, and as a result, cyanidin and peonidin significantly promoted neurite outgrowth elongation. And also, the increase of histone acetylation in SH-SY5Y cells treated with anthocyanidins was confirmed.

Next, for the anthocyanins confirmed Hdac inhibitory activity, we examined the influence on nematode life span. As a results, Delphinidin, peonidin and petunidin significantly extended lifespan. And we investigated the effect of histone acetylation on lifespan by using a mutant (defective strain) of a nematode homologue (hda-2, 3, 4, 10) of human Hdac gene. It is suggested that the lifespan extension effect of delphinidin, peonidin and petunidin may be epigenetic regulation via hda - 3, hda – 2, 3, 10, and hda - 2, 3, 4, 10, respectively.

Our result suggests that neuroprotective, neurite outgrowth and anti-aging effect by anthocyanins may be undergoing epigenetic regulation via HDAC activity.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R00 AG034989
NIH Grant T32 NS061788
Civitan International

Title: Klotho regulates the activity of hippocampal neurons

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Abstract: Klotho (KL) is a protein that is age-downregulated across species and predominantly expressed in the brain and kidney. It is known for its profound effects on lifespan where KL

deficient mice exhibit significantly reduced lifespan concurrent with a variety of human-like aging phenotypes, while KL overexpressing mice exhibit extended lifespan. Along with these effects on lifespan, KL expression level also regulates cognition. In mice, this is most well characterized using hippocampus-dependent behavioral assays where KL-deficient mice rapidly develop cognitive impairment early in life in a gene dose dependent manner. Meanwhile, both KL overexpressing mice and humans carrying a polymorphism that elevates KL expression are cognitively enhanced. In mice, KL overexpression is specifically protective against age-related cognitive decline. These data suggest that KL is important for maintaining cognitive function with age. We recently reported that KL is expressed in pre- and post-synaptic compartments of hippocampal neurons and regulates synaptic plasticity. In that report, we found paradoxical dissociations between long-term potentiation and cognitive function in both KL-deficient and overexpressing mice. Here, we seek to understand molecular mechanisms underlying this effect by investigating the effects of KL on neuronal morphology and homeostatic plasticity. The morphology of neurons from these mice was assessed by performing Sholl and spine analyses on apical dendrites of CA1 pyramidal neurons using three biological replicates and analyzing in excess of 1000µm of dendritic segments. Multi-electrode array recordings of cultured neurons across three biological replicates and at least two technical replicates per experiment was used to assess neuronal activity and the ability to induce homeostatic plasticity. Our results suggest that the increased LTP in cognitively impaired KL-deficient mice may be the result of neuronal hyperactivity and KL dependent changes in spine morphology. Together these data suggest that KL is an important regulator of neuronal activity and that changes in KL expression may impinge on network activity in the hippocampus to affect cognition. KL-deficiency occurs with age suggesting that KL is vital to maintain cognitive function in aging brains.

Disclosures: H.T. Vo: None. M.L. Phillips: None. J.H. Herskowitz: None. G.D. King: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.15/L10

Topic: C.01. Brain Wellness and Aging

Support: NSERC RGPIN-2017-05392
Pharmaqam Research Center

Title: Characterization of interaction between ubiquitin ligase RNF167 and ubiquitin conjugating enzyme Ube2N

Authors: K. GHILARDUCCI, C. DESROCHES, B. DJERIR, J. ARTEAU, L. EL CHEIKH-HUSSEIN, *M. P. LUSSIER
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Abstract: The mammalian brain relies on its ability to precisely regulate the function of synapses in order to achieve various tasks such as memory formation and learning. Current knowledge regarding the mechanisms that govern the excitability of the synapses limits our understanding to solve, for example, the foundations of memory. In this context, the focus of our laboratory is to uncover the molecular and cellular determinants that regulate the synaptic abundance of AMPA-type glutamate receptor (AMPA) at hippocampal synapses. Several recent studies indicate that the addition of ubiquitin molecules on AMPAR dynamically control its intracellular trafficking and synaptic expression. Accordingly, the E3 ubiquitin ligase (UBE3) RNF167 is an endosomal RING-type UBE3 that negatively regulates the synaptic expression of AMPARs. However, the mechanism by which RNF167 controls AMPARs remains unclear and the scarcity of information regarding the molecular mechanisms key to RNF167 activity currently impedes our ability to accurately pinpoint its cellular function. Moreover, the role played in the brain by the ubiquitin-conjugating enzymes (UBE2) functionally pairing with UBE3s such as RNF167 has received little attention. Thus, elucidating the function of UBE2-RNF167 pairs in the brain will be especially informative to understand the specificity of the reaction toward a substrate protein such as AMPARs. To identify putative UBE2 interacting with RNF167, an in vitro ubiquitination assay with recombinant RNF167 was performed. From the possible 29 UBE2 candidates tested, UBE2N (UBC13) functionally interacts with RNF167. Notably, UBE2N catalyzes K63 poly-ubiquitin chain, a type of ubiquitin chain recently described to control AMPAR trafficking. In vitro binding assays and Surface Plasmon Resonance further confirmed the interaction between UBE2N and RNF167. Significantly, the SPR assay demonstrates that the measured affinity between RNF167 and UBE2N is in accordance with biologically relevant transient interaction. Lastly, immunofluorescence in heterologous cells as well as specific immunoblots of proteins isolated from subcellular fractionation of mice cortices show that RNF167 and the UBE2N are located in the same cellular compartment. Overall, this study identified UBE2N as a functionally interacting partner of RNF167 and may thus offer a first glimpse into the underlying mechanism by which RNF167 controls AMPAR-mediated neurotransmission.

Disclosures: **K. Ghilarducci:** None. **C. Desroches:** None. **B. Djerir:** None. **J. Arteau:** None. **L. El Cheikh-Hussein:** None. **M.P. Lussier:** None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.16/L11

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01MH103374

Title: Unraveling the role of the WASH complex in neurological dysfunction

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Abstract: Emerging evidence suggests that mediators of protein trafficking may be critical to movement and cognitive disorders. One complex thought to regulate protein trafficking to endosomes is the WASH complex. WASH is recruited to endosomes by the retromer complex, where it facilitates the budding of cargo from endosomes. Interestingly, mutations within WASH complex components (Strumpellin and SWIP), as well as mutations in the retromer complex are associated with movement and cognitive disorders such as Parkinson's disease, hereditary spastic paraplegia, and intellectual disability. However, how these mutations manifest in neurological dysfunction is currently unknown. To address these questions, we have generated mice with WASH complex mutations to decipher the contribution of WASH members to neuronal function. Using proteomic, histological, and behavioral assays, we find that disturbance of the WASH complex produces both motor impairments and cognitive deficits in mice. Our work provides evidence that WASH complex-dependent protein trafficking is a driver of pathophysiology relevant to neurodegenerative disorders, providing a new avenue for future therapeutic endeavors.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

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Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG020494
NIH Grant AG027956

Title: Predictors of estrogen's neuroprotective efficacy

Authors: *J. TOOFAN¹, C. SU¹, N. SUMIEN², M. SINGH³

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Abstract: The precipitous decline in ovarian hormones after the menopause may put women at greater risk for age-associated cognitive decline and serves as the basis for considering hormone therapy to support brain health. However, equivocal results from clinical trials underscore the need to better understand the neurobiology of these steroid hormones. Data from our lab show

that treatment of young ovariectomized (OVX) rats with 17beta-estradiol (E2) increases brain-derived neurotrophic factor (BDNF) mRNA expression in the hippocampus. However, in middle-aged animals, the effect of E2 was diminished, supporting the existence of an age-dependent window of opportunity for these hormones. In this study, we evaluated the expression of BDNF and other relevant molecular markers of cognition in young and middle-aged female ovariectomized (OVX) Sprague Dawley rats to determine if possible age-associated changes in their expression was correlated with the response to estrogen. Real-time PCR was used to evaluate the expression of BDNF, TrkB, p75, and RbAp48 mRNA in the hippocampus of 4 month- and 10 month-old OVX Sprague Dawley rats. We found that TrkB and RbAp48 in hippocampal mRNA are significantly decreased in middle-aged OVX rats as compared to young OVX, suggesting that indeed, there are changes in relevant molecular markers of cognitive function with age, that in turn, could diminish the protective effects of E2. Given reports from other labs showing that changes in estrogen receptor (ER)-alpha expression may influence the response of the hippocampus to E2, we also conducted studies *in vitro* to determine which ERs are critical to mediating the effects of E2 on BDNF. The effect of E2 (10nM, 24 hours) on BDNF mRNA expression was evaluated in ER-alpha transfected, differentiated SH-SY5Y cells. In parallel, we also performed immunocytochemistry to allow for single-cell based analysis of non-transfected cells vs. transfected cells in terms of their response to E2. Furthermore, we evaluated the effect of E2 on cell viability (using the MTT assay). Our data revealed that E2 treatment of ER-alpha - transfected SH-SY5Y cells did not exhibit significant increases in BDNF mRNA or protein, nor did it protect the cells from amyloid-beta-induced cytotoxicity. These studies suggest that ER-alpha, alone, may not be a critical mediator of E2's beneficial effects on cognition.

Disclosures: J. Toofan: None. C. Su: None. N. Sumien: None. M. Singh: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

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Program #/Poster #: 044.18/L13

Topic: C.01. Brain Wellness and Aging

Support: HHMI
EMBO Long Term Fellowship

Title: Progressive loss of neuron identity and function through a cis-regulatory mutation

Authors: *E. LEYVA-DÍAZ^{1,2}, O. HOBERT^{1,2}

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Abstract: Mutations in non-protein-coding, *cis*-regulatory control regions have become widely appreciated as potential drivers of human disease, but it has proven challenging to associate

putative regulatory mutations with functional readouts. To shed light on the putative relevance of *cis*-regulatory mutations in the context of neurodegenerative conditions, we used the CRISPR/Cas9 system to engineer a *cis*-regulatory mutation in the *che-1* locus of the nematode *C. elegans*. *che-1* encodes a terminal selector-type zinc finger transcription factor that is required to initiate the terminal differentiation program of a gustatory neuron class, ASE, during embryonic development. We find that the removal of an autoregulatory motif of the *che-1* promoter does not disrupt early specification of the ASE neuron class in the embryo, but leads to a progressive loss of ASE molecular features and function in larval stages. Adult animals display a “metastable” condition, in which *che-1* expression is completely lost in some individuals while maintained at low levels in others, revealing a variably penetrant destabilization of transcription factor expression. As such, ASE molecular features and neuronal function are completely lost in certain individuals while severely reduced in others. These results demonstrate that neuronal identity maintenance is compromised in adult stages when the sustained expression of the terminal selector is disrupted. In our model, initiation of terminal selector gene expression is triggered through transient regulatory inputs, which feed into the terminal selector locus via *cis*-regulatory elements that are separate from the autoregulatory elements that ensure maintenance after the initial ‘kick off’ phase. Therefore, terminal selector autoregulation, which ensures a sustained TF expression through life, is required for neuronal identity maintenance and function of a *C. elegans* gustatory neuron. The progressive worsening of phenotype over time suggests that *cis*-regulatory mutations of neuron identity controlling regulatory factors could potentially be the underlying cause of adult-onset degenerative conditions in humans.

Disclosures: E. Leyva-Díaz: None. O. Hobert: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

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Topic: C.01. Brain Wellness and Aging

Support: USC Graduate Student Fellowship

Title: Novel mechanisms of protein homeostasis in muscle and neurons

Authors: *M. MORI, P. HAGHIGHI
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Abstract: Disruption of proteostasis is a hallmark of aging and many age-dependent neurodegenerative disorders, including Alzheimer's Disease and Parkinson's Disease. Discovering mechanisms that regulate and promote proteostasis therefore is critical for opening new avenues in combatting age-dependent neurodegeneration. Using the genetic tools available

in *D. melanogaster*, we have identified a member of ABC transporter family as a novel contributor to maintaining age-dependent proteostasis by assaying for polyubiquitinated proteins as indicator of proteostatic health. We demonstrate the heterozygosity for the ABC transporter is sufficient to increase the level of age-dependent accumulation of polyubiquitinated protein aggregates. Tissue-specific knockdown of the ABC transporter disrupts proteostasis in both muscle and brain, indicating a cell-autonomous role of the transporter in inhibiting protein aggregate accumulation. Analysis of interacting partners of the ABC transporter suggest that the role of the transporter in amino acid uptake and the subsequent amino acid metabolism may contribute to reducing age-dependent accumulation of protein aggregates. Our preliminary results demonstrate a novel role of ABC transporters in promoting proteostasis. We are exploring the role of dietary amino acids and metabolites in regulating proteostasis, and investigating whether the ABC transporter promotes protein homeostasis in several neurodegeneration models, including amyloid-beta and poly-glutamine aggregates.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.20/L15

Topic: C.01. Brain Wellness and Aging

Support: Center for innovative medicin (CIMED) Sweden

Title: Investigating the biological mechanisms underlying alterations in cognition from the multimodal intervention study FINGER

Authors: *A. SANDEBRING¹, L. PATERNAIN-MARKINEZ¹, J. GOICOLEA¹, I. BJÖRKHEM², A. SOLOMON¹, M. KIVIPELTO¹, A. CEDAZO-MINGUEZ¹
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Abstract: Rationale: The multimodal intervention strategy tested in the FINGER trial showed very promising results in elderly at risk for dementia. After the 2-year follow-up there was a significant improvement in the intervention group. In the current study we wanted to elucidate the relationship between cardiovascular risk factors such as cholesterol and its oxygenated derivative 27-hydroxycholesterol for glucose uptake in the brain. Methods: We utilized mass spectrometry to determine the levels of serum cholesterol, 27-hydroxycholesterol (27-OH) and 24-hydroxycholesterol (24-OH) in a subset of the FINGER participants that had been deeper characterized by positron emission tomography and magnetic resonance (PET) imaging. We used STATA to analyze the data-set. Results: Compared to total cholesterol levels, 27-OH had a

stronger correlation with high systolic blood pressure, low glucose uptake in the brain and a high level of white matter hyper-intensities. Conclusions: The epidemiological risk factors for AD are not always easily translated into molecular mechanisms in the cell. Cardiovascular risk factors contribute greatly to AD risk, still our understanding of the underlying mechanisms is not well characterized. The current study show that 27-OH may be an important risk factor for decreased cognitive function in elderly. Gaining a deeper understanding of the mechanisms involved in the FINGER study may not only improve the design of interventions but also contribute to the exploration of new drug targets for AD.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 044.21/L16

Topic: C.01. Brain Wellness and Aging

Support: NIH K01 Grant to H. Lawal
NIH/COBRE Grant, M. Harrington (PI)

Title: Point mutations in the vesicular acetylcholine transporter alter behavioral performance during *Drosophila* lifespan

Authors: ***H. O. LAWAL**, J. MURPHY, S. WILLIAMS, Y. MARTINEZ
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Abstract: Acetylcholine (ACh) neurotransmission is crucial in the regulation of locomotion and learning and memory. Consequently, the dysregulation in this neurotransmitter system has been identified as an important contributor to locomotor and cognitive deficits. However, the mechanism through which this process occurs remains unclear. Another challenge in the field is a lack of understanding of the precise role that ACh neurotransmission plays in the behavioral decline that is seen during aging. The vesicular acetylcholine transporter (VAcHT) regulates the translocation of ACh into synaptic vesicles for release at the plasma membrane. And while much is known about how this protein executes its transport function, comparatively less is known about the consequences of this activity on ACh-mediated behaviors such as locomotion throughout the lifespan of an organism. Here we sought to test the hypothesis that point mutations in *Vacht* will cause age-related deficits in cholinergic-mediated behaviors such as locomotion. We are characterizing several point mutations in *Vacht* for their survivorship and their locomotion ability across the lifespan. We report that *Vacht* mutations cause a differential effect on survivability in a manner that depicts an allelic series. We also show that these

mutations cause differential deficits in locomotion performance with the onset of aging. Moreover, we present preliminary results of a study to measure aging in the *Vacht* point mutations tested using the “smurf assay” an important metabolic marker of that process. These findings help highlight the importance of ACh on behavioral performance during aging and represents one of the first in vivo demonstrations of a clear role of VAcHT in aging.

Disclosures: H.O. Lawal: None. J. Murphy: None. S. Williams: None. Y. Martinez: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

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Topic: C.01. Brain Wellness and Aging

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CTSC #UL1-RR024996
NIH G12 RR003037

Title: Proteasome function in the longevity *Drosophila* mutant methuselah

Authors: *T. SCHMIDT-GLENEWINKEL, J. GAO, C.-H. YEH, M. FIGUEREIDO-PEREIRA

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Abstract: Many neurodegenerative diseases are associated with the formation of protein aggregates. The accumulation of aggregated proteins in form of neurofibrillary tangles and senile plaques in Alzheimer disease (AD) suggests that inability to turnover or degrade certain proteins might be a key factor in the etiology of certain neurodegenerative disorders, like Alzheimer disease. Degradation of most proteins is normally carried out via ubiquitination followed by degradation by the proteasome. Impairment of the ubiquitin proteasome pathway (UPP) may therefore be a contributing factor in the etiology of neurodegeneration. Here we report the results of our studies comparing proteasome activity and ATP levels in wild type and the longevity mutant methuselah (*mth*) of *Drosophila*. *Mth* displays lower proteasome activity, lower proteasome levels and lower ATP steady state levels at young ages when compared with wild type, but higher levels at old ages during normal aging, when compared with control strain *w1118*. Furthermore, *mth* formed fewer ubiquitinated protein aggregates across ages under normal aging, as well as under oxidative stress conditions. Moreover, while both strains exhibited a gradual increase in ubiquitinated protein conjugates with aging, *mth* produced fewer conjugates at the comparative ages as *w1118*. Under oxidative stress conditions, ubiquitinated conjugates level was elevated in both strains, but less conjugates was observed in *mth*.

Furthermore, mth formed fewer ubiquitinated protein aggregates across ages under normal aging, as well as under oxidative stress conditions.

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Poster

044. Brain Wellness and Aging: Molecular Mechanisms

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Program #/Poster #: 044.23/L18

Topic: C.01. Brain Wellness and Aging

Support: VA Grant 1I01BX003303-01

Title: Biogenetic features and function of the mitochondrial ribosome in health and mitochondrial encephalomyopathies

Authors: *A. K. CHOI^{1,2}, A. BARRIENTOS², H. ZHONG²
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Abstract: Defects in oxidative phosphorylation (OXPHOS) cause a heterogeneous and often devastating group of disorders known as mitochondrial diseases which commonly feature central nervous system dysfunction and neuropathy. Mitochondrial diseases are poorly understood, and treatment options are almost-entirely symptomatic. A subset of these diseases is caused by mutations in essential components of the mitochondrial translation machinery, which is maintained exclusively for the synthesis and co-translational insertion of thirteen protein components of the OXPHOS enzymatic complexes into the inner-mitochondrial membrane (IMM). This machinery includes the mitochondrial ribosome, which has diverged substantially from its better understood cytosolic and bacterial counterparts through major structural and compositional modifications. Despite apparent importance for productive assembly of the OXPHOS complexes, little is known about how mitoribosome specific adaptations regulate its function. The **objective** of this project is to expand our understanding of how mitoribosome biogenesis, composition, and structure affect its function in the context of health and disease. Our research focuses on a unique aspect of the mitoribosome: its tethering to the IMM. Based on high resolution mitoribosome structures, this tethering is thought to be mediated by the mitoribosome large-subunit (mt-LSU) protein mL45, which we hypothesize functions in appropriate insertion of nascent polypeptides into the IMM making it critical to OXPHOS complex assembly. We will test this hypothesis with both an exploratory and confirmatory approach to the following aims: **Aim I**) Characterize the role of mL45 in mitoribosome assembly and function; **Aim II**) Define structural determinants of the mL45-mediated anchorage to the IMM; **Aim III**) Define components of the mL45 mitoribosome anchoring site. Our **methodology**

involves examination of the structure-function relationship of mL45 in terms of mitoribosome assembly and function through expression of strategically modified versions of mL45 in human cancer cell lines deficient in mt-LSU assembly or ablated for mL45. We will search for additional mitoribosome tethering mediators by identifying the mL45 interactome using co-ImmunoPrecipitation approaches and BioID proximity labeling followed by mass spectrometry. All experiments will be performed at least in triplicate. Early results show that mL45 is necessary for the stability of mt-LSU proteins, mt-LSU assembly, and translational function of the mitoribosome. Ongoing work will reveal a more detailed picture of mL45's contribution to mitoribosome assembly and function.

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Poster

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Topic: C.01. Brain Wellness and Aging

Support: 1189541-100-UAHMG

Title: A mitochondrial membrane-spanning ternary complex regulates mitochondrial motility

Authors: *L. LI¹, X. WANG²

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Abstract: Cells regulate mitochondrial movement and dynamics to maintain energy homeostasis and prevent oxidative stress. The anterograde microtubule-dependent mitochondrial transport is mediated by a motor/adaptor complex that includes Milton, Miro, and the kinesin heavy chain. Miro is inserted into the outer mitochondrial membrane (OMM) and relays diverse cellular signals to mitochondria to control their movement and quality. It has been established that Miro degradation in proteasomes is primed by PINK1/Parkin-dependent phosphorylation and ubiquitination. However, Miro is an OMM integral protein and would require a regulatory mechanism to extract it from the membrane following these posttranslational modifications. We therefore screened the cellular and molecular factors that may regulate Miro removal from the OMM. We discovered a novel molecular machinery spanning both the mitochondrial outer and inner membranes that glues Miro to the OMM from the inside and thus stabilizes Miro. Knockdown of each component of this ternary complex reduces the axonal transport of mitochondrion. Moreover, this novel machinery and regulation responses to the different metabolic signals and stressors, therefore acting as an important biomarker for health and disease.

Disclosures: L. Li: None. X. Wang: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.25/M2

Topic: C.01. Brain Wellness and Aging

Support: NIA AG047652 to WHG

Title: Inhibition of synaptic transmission by the antidepressant amitriptyline in basal forebrain neurons from young and aged vGAT-ChR2-eYFP mice using patch-clamp electrophysiology and optogenetic light stimulation

Authors: *E. BANG, A. TOBERY, D. A. MURCHISON, D. W. DUBOIS, K. S. MONTGOMERY, W. H. GRIFFITH
Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Depression is one of the most common psychiatric disorders in clinical medicine and often is associated with cognitive impairment during aging. Our lab has been studying age-related effects of therapeutic drugs on synaptic transmission and intracellular calcium homeostasis using whole cell patch-clamp, ratiometric calcium indicators and light-evoked stimulation in behaviorally characterized rodent models. Amitriptyline is a well-known antidepressant drug used to treat clinical depression, however it has not been studied extensively in aging models. Previous work from our lab has shown that amitriptyline decreased HVA calcium currents more in aged rat basal forebrain (BF) neurons compared to young. The purpose of this study is to test whether the well-established channel blocking actions of amitriptyline might exacerbate an age-related disruption of synaptic transmission in the BF using young (1-7 mo) and aged (>21 mo) vGAT-ChR2-eYFP mice. We used whole cell patch-clamp recording from a reduced synaptic preparation of mouse BF neurons expressing channelrhodopsin-2 under the control of the vesicular GABA transporter promoter to study light-activated inhibitory postsynaptic currents (IPSCs). Neurons were identified as either GABAergic or cholinergic using real time single-cell RT-PCR. We report that amitriptyline (3 μ M) significantly decreased the amplitude of light-evoked IPSCs (65%, n=21) and reduced the quantal content (77%, n=21) of GABA release from presynaptic terminals in both GABAergic and cholinergic neurons from young mice. The frequency of spontaneous IPSCs was reduced also in both young (51%, n=8) and aged (62%, n=7) neurons. Experiments are in progress to extend these findings using the Barnes maze test to identify aged cognitively impaired and unimpaired subjects. These results suggest that amitriptyline block of Ca²⁺ channels on presynaptic GABAergic neurons reduces inhibitory synaptic transmission in the BF. Because decreased inhibitory synaptic transmission in

BF is associated with age-related cognitive impairment in rats, antidepressants that augment this decrease could have unintended impacts on cognition in the elderly.

Disclosures: E. Bang: None. A. Tobery: None. D.A. Murchison: None. D.W. DuBois: None. K.S. Montgomery: None. W.H. Griffith: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.26/M3

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant AG047652 to WHG

Title: A novel optogenetic mouse model for aging in basal forebrain neurons of ChR2-eYFP (vGAT) BAC mice: Alterations in synaptic physiology, calcium homeostasis and cognition

Authors: *K. S. MONTGOMERY, D. W. DUBOIS, E. BANG, A. S. FINCHER, D. W. MURCHISON, W. H. GRIFFITH
Neurosci. & Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Our lab has described consistent and robust age-related changes in calcium homeostasis and synaptic physiology, as well as cognitive decline in a Fischer 344 rat model of aging (Murchison et al, 2009; Griffith et al., 2014). We have established an aging colony of vGAT-ChR2 (H134R)-eYFP BAC mice that mirrors the previous rat model, and enables utilization of breakthrough technologies in mouse genetics and optogenetic neural stimulation. We used whole cell patch-clamp in acute brain slices and in a reduced synaptic preparation of mouse basal forebrain (BF) neurons expressing channelrhodopsin-2 (ChR2) under the control of the vesicular GABA transporter promoter. We studied light-activated ChR2 currents and spontaneous and light evoked inhibitory postsynaptic currents (IPSCs). Light-induced ChR2 currents (measure of functional expression) were unaltered from 3-24+ months: (peak current density, pA/pF: young: 4.6 ± 1.4 pA/pF, middle: 3.2 ± 0.6 pA/pF, aged: 4.2 ± 0.6 pA/pF; n = 6-11). As in rat, the frequency of spontaneous IPSCs in mice decreased with age (mean \pm SE, Hz: young: 0.992 ± 0.271 ; aged: 0.49 ± 0.091), and could be rescued to control frequencies by depolarization of the presynaptic terminal with 10 mM K⁺ (0.9383 ± 0.251 Hz). Optogenetic IPSCs were evoked using brief light pulses (2-5 ms) in BF slices of vGAT-ChR2 mice. There was a decrease in IPSCs amplitude with age: young (3-7 mo), 37.5 ± 5.1 pA/pF; aged (18-24+ mo), 22.3 ± 4.7 pA/pF, n = 17-40 (p = 0.04). We also find a significant increase in intracellular buffering in BF neurons from aged mice which parallels previous findings in aged rat BF neurons. We assessed cognitive status in mice using the Barnes maze spatial task. In the first week of training we observed that aged mice travelled longer distances to reach the target hole

($p < 0.0001$). The same was observed during reversal trials ($p < 0.0001$). Performance on the last day of reversal trials shows the variability and separation of cognitively impaired versus unimpaired aged subjects very much like the rat aging model in the Morris water maze (Griffith et al., 2014). These results demonstrate that these optogenetic BAC mice are excellent models of aging and demonstrate all of the features of previous aging rat models.

Disclosures: D.W. DuBois: None. E. Bang: None. A.S. Fincher: None. D.W. Murchison: None. W.H. Griffith: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.27/M4

Topic: C.01. Brain Wellness and Aging

Title: The neurodevelopmental consequences of genomic stress

Authors: *N. MICHEL¹, U. MAJUMDAR², M. J. MCCONNELL²

¹Neurosci. Grad. Program, ²Biochem. and Mol. Genet., Univ. of Virginia, Charlottesville, VA

Abstract: The abnormal accumulation of DNA damage in neurons is a shared pathological feature among neurodegenerative diseases (Alzheimer's disease, Parkinson's disease) and it is also correlated with normal aging. Transgenic mouse models further demonstrate a specific requirement for DNA repair during neurogenesis. It is also known that genomic stress, arising from ongoing transcription and metabolic byproducts, plays a role in aging because it contributes to the accumulation of DNA damage. Previously, studying aging in the human brain has been incredibly challenging; post-mortem tissue is difficult to acquire and is not amenable to longitudinal studies. Furthermore, studies of aging have typically looked at model organisms later in life, meaning that few have assessed how stress exposure impacts the development of the brain and how that ultimately affects the aging process.

With the development of human-induced pluripotent stem cells (hiPSCs), we now have an *in vitro* model of human neurodevelopment that provides a tool to study models of normal and pathological neurodevelopment. The goal of this study is to determine how genomic stress and subsequent DNA damage alters the diversity among hiPSC-derived neural progenitor cells (NPCs) and their progeny. Our work examines how NPCs respond to genomic stress and whether that response differs from isogenic fibroblasts and hiPSCs. NPCs are particularly susceptible to transcription associated genomic stress and have alteration in NPC fate decisions. Ongoing experiments will examine if genomic stress alters neuronal diversity through single cell RNA-seq. hiPSC-based neurogenesis provides a human model system to understand genomic stress related mechanisms in aging and neurodegeneration. Defining how neurodevelopmental stress may predispose subsets of neurons for later neurodegeneration will ultimately lead to

consequent studies focused on protecting NPCs and their progeny from genomic stress to prevent accelerated aging and neurodegenerative disease.

Disclosures: N. Michel: None. U. Majumdar: None. M.J. McConnell: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.28/M5

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

Support: NUHSRO/2018/016/T1

Title: Human amylin promotes the pathogenesis of Alzheimer's disease

Authors: *Y.-A. A. LIM, W. LEE, P. T. H. WONG, T. V. ARUMUGAM
Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Alzheimer's disease (AD) is the most common form of dementia with no disease-modifying treatments, and current therapies only provide temporary symptomatic relief. Epidemiological studies have established Type 2 diabetes (T2DM) as a risk factor of AD, but the underlying mechanisms remain unresolved. Clinically, AD is characterized by the presence of amyloid-beta plaque deposition and neurofibrillary tangles in the brain. Recent reports show that human amylin (HA) peptide, that aggregates to form plaques in T2DM pancreas, is also deposited in the brains of AD and diabetic brains. The NLRP3 inflammasome has recently been shown to play a major role in neurodegeneration in MCI and AD brains and mediates HA-induced toxicity in the T2DM pancreas. However, whether the NLRP3- inflammasome mediates HA-induced neurotoxicity in the brain remains to be formally investigated. Caspase-1 is a known effector of NLRP3 inflammasome activation. Analysis of human brain samples and cell culture experiments indicate that HA induces neuronal toxicity via the NLRP3-caspase-1 axis and promotes the accumulation of amyloid-beta in the brain. Furthermore, the use of a caspase-1 specific inhibitor abolishes the accumulation of amyloid-beta, suggesting that amyloid-beta accumulation is regulated at least in part via inflammasome activation. Our work supports the further assessment of caspase-1 inhibition as a novel therapeutic treatment strategy for AD.

Disclosures: Y.A. Lim: None. W. Lee: None. P.T.H. Wong: None. T.V. Arumugam: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.29/M6

Topic: I.07. Data Analysis and Statistics

Support: Regional grant Midi-Pyrénées FLUIDBRAIN
ERC consolidator grant 615102 BRAINMICROFLOW

Title: Biomechanical approach of brain aging, neurodegenerative diseases and frailty

Authors: *A. VALLET¹, A. LOKOSSOU², S. LORTHOIS³, P. SWIDER³, P. ASSEMAT³, L. RISSER⁴, Z. CZOSNYKA⁵, M. CZOSNYKA⁵, N. DEL CAMPO⁶, L. BALARDY⁶, P. PERAN¹, O. BALÉDENT², P. PAYOUX¹, E. SCHMIDT^{1,6}

¹ToNIC, INSERM, Toulouse, France; ²CHIMERE, Amiens, France; ³Inst. de Mécanique des Fluides de Toulouse, ⁴Inst. de Mathématiques de Toulouse, Ctr. Natl. De La Recherche Scientifique, Toulouse, France; ⁵Neurosurv. Unit, Department of Clinical Neurosciences, United Kingdom; ⁶Ctr. Hospitalier Universitaire de Toulouse, Toulouse, France

Abstract: Brain aging is a natural process, however it can become pathological due to biological, biochemical and biomechanical stresses affecting the brain, leading to neuronal loss and neurodegenerative diseases. We propose to explore the frail zone that is the transition region from normal to pathological brain aging with a biomechanical approach. Parameters such as resistance and elastance are related to the brain structure and cerebral fluids dynamics [1]. The brain elastance, in particular, describes the brain ability to accommodate to volume changes. **Our hypothesis is that the identification of biomechanical properties of the brain can contribute to the objective quantification of the shift from normal to pathological brain aging.**

A statistical analysis was performed on the PROLIPHYC database [2] that included 100 patients with enlarged ventricles or parenchymal atrophy, gait disturbance, modest cognitive decline or urinary incontinence. Using the SEGA score of frailty [3] - based on cognitive status, nutritional status, risk of depression, level of independence and fall risk [3] - 47 % of the patients were classed as not very frail, 34 % as frail, and 19 % as very frail.

The cerebrospinal fluid (CSF) dynamics was explored using an infusion test. The intra cranial pressure (ICP) was recorded while a saline fluid was injected at constant rate through a lumbar puncture. The intracranial fluids (blood and CSF) dynamics were also quantified (at baseline) with phase contrast MRI. A mathematical model of the blood and CSF circuit system [4] was fitted on the clinical measurements in order to obtain the apparent brain mechanical properties (elastance, CSF production rate, resistance to CSF outflow, venous pressure and vascular compliance).

The statistical analysis showed a significant correlation ($r=0.34$, $p=0.01$) between elastance and frailty index SEGA. This supports our hypothesis that biomechanical characterization of the brain could be valid to identify the transition from normal to pathological aging. To interpret further this observation, a study is planned to analyse the relationship between the brain elastance and the structural alterations, like ischemic lesions, quantified on MRI.

[1] Goriel, 2015 Biomech Model Mechanobiol. [2] PHRC 10-0458-08, clinicaltrials NCT02016352 [3] Oubaya 2014 J Nutr Health Aging [4] Czosnyka 2004 Physiol Meas.

Disclosures: **A. Vallet:** None. **A. Lokossou:** None. **S. Lorthois:** None. **P. Swider:** None. **P. Assemat:** None. **L. Risser:** None. **Z. Czosnyka:** None. **M. Czosnyka:** None. **N. Del Campo:** None. **L. Balardy:** None. **P. Peran:** None. **O. Balédent:** None. **P. Payoux:** None. **E. Schmidt:** None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.30/M7

Topic: C.01. Brain Wellness and Aging

Support: NSF RUI 1748523

Title: Characterizing the role of autophagy gene product BEC-1 in neuronal longevity in the model organism *Caenorhabditis elegans*

Authors: *N. ASHLEY, H. TROMBLEY, A. HOLGADO
Biol. Sci., St. Edward's Univ., Austin, TX

Abstract: Aging can be defined by many different physiological pathways that emphasize changes in a variety of cells and tissues. Central Nervous System (CNS) neural networks have been important for understanding cellular processes that cause aging, which is partly characterized by cell death and can be observed as a result neurodegenerative diseases such as Parkinson's Disease (PD). Previous studies have identified defects in autophagy, a cellular housekeeping mechanism that recycles products via degradation, results in neuron degeneration. Specifically, autophagy gene product BEC-1 has been characterized as essential for autophagy induction. We hypothesize that neuronal longevity will be affected in animals lacking BEC-1, suggesting an important role of autophagy in neuronal survival. Examination of *Caenorhabditis elegans* (*C. elegans*) with the *bec-1(ok691)* mutation and balancer nT1 showed that the majority of homozygous *bec-1(ok691)* mutants are embryonic-larval lethal. Preliminary studies of heterozygous and marginal surviving homozygous *bec-1(ok691)* mutants showed significant defects in backward locomotion, longevity, and neuronal survival. Additionally, motility assays performed using an eyelash demonstrated that homozygous *bec-1(ok691)* mutants have defective

backwards locomotion after nose-touch. Future research will include construction of a strain containing the *bec-1(ok691)* mutation and expressing neuronal LGG-1 fused to a double fluorescent protein and a marker for d-type motor neurons. The integrated transgene *SoIs5* codes for the expression of CERULEAN::VENUS::LGG-1 on autophagosomes. Transgene *wplIs36* contains *unc-47p::mcherry*, thus, localizing to d-type motor neurons. Quantification of autophagy and neuronal survival will be studied in this strain.

Disclosures: H. Trombley: None. A. Holgado: None.

Poster

044. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 044.31/M8

Topic: C.01. Brain Wellness and Aging

Support: NSF RUI 1748523

Title: Investigating the role of autophagy in axonal development in *unc-33* mutant *C. elegans*

Authors: *M. N. WILSON, R. FIRTH, A. SANCHEZ, H. TROMBLEY, A. HOLGADO
St. Edward's Univ., Austin, TX

Abstract: Autophagy is a self-degradative mechanism used within cells to maintain homeostasis in recycling cellular waste and protein aggregates through an autophagosomal-lysosomal system. The induction of autophagy has been implicated in regulating axonal development via CRMP-2/UNC-33/Dpysl2, a neuronal protein that accumulates within the neurites and research suggests it serves a key role in neuronal development. To properly evaluate the relationship between autophagy and axonal development, the aim of this study is to induce autophagy in *unc-33* mutants and study the effects on axonal development. Induction of autophagy will be stimulated via starvation. Transgenic nematodes possessing a dual fluorescently tagged (dFP) LGG-1 and a marker for D-type motor neurons in *unc-33* mutant backgrounds were constructed to allow for the observation of levels of autophagy and rescue. The dFP tagged LGG-1 was used to monitor the flux of autophagy by quantifying the cleavage of the dFP into monomeric fluorescent protein upon arrival at the lysosome. The fluorescent marker for D-type motor neurons will be used to monitor the neuronal circuitry in the presence or lack of UNC-33. Preliminary data shows that *unc-33* null mutants have increased autophagy as measured by LGG-1/puncta density in the nerve ring and cleavage of dFP tagged LGG-1 protein. Analysis of neuronal circuitry under induced autophagy is currently being performed. Together the data suggest that lack of UNC-33 gene product results in a further induction of autophagy in the absence of nutrients.

Disclosures: M.N. Wilson: None. R. Firth: None. A. Sanchez: None. H. Trombley: None. A. Holgado: None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.01/M9

Topic: B.06. Synaptic Transmission

Support: NIH AG051593
NIH AG054176
NIH AG055247

Title: Clinical evidence of synaptic protection in Alzheimer's patients following treatment with CT1812

Authors: *S. M. CATALANO¹, N. J. IZZO², K. MOZZONI², C. SILKY², C. REHAK², M. GRUNDMAN³

¹Cognition Therapeut. Inc., Pittsburgh, PA; ²Cognition Therapeutics, Inc., Pittsburgh, PA;

³Global R&D Partners LLC, San Diego, CA

Abstract: CT1812 (ElaytaTM) is the only therapeutic candidate demonstrated to displace A β oligomers from synaptic receptor sites and clear them from the brain into the CSF, restoring synapse number and cognitive performance to normal in aged transgenic mouse models of AD. Synaptic degeneration is observed early in Alzheimer's disease and cognitive performance correlates most closely with synapse number. In a Phase 1b/2a clinical trial, mild to moderate (MMSE 18-26) Alzheimer's patients (N=19) were randomized to one of three doses of CT1812 (90, 280 or 560 mg Q.D.) or placebo given orally once daily for 28 days (4 weeks) to determine safety, tolerability, and PK. Exploratory outcomes included CSF protein expression measured via lumbar puncture at baseline (Day 0) and end of treatment (Day 28). CSF concentrations of neurogranin and synaptotagmin-1, synaptic proteins important for normal synaptic function and plasticity, are elevated 27% and 52% respectively in AD patients compared to controls as a result of CNS synaptic damage due to the disease (Janelidze, et al. 2016; Ohrfelt, et al. 2016). We measured concentrations of these synaptic damage biomarkers in CSF samples from AD patients taken at baseline and after 28 days of CT1812 treatment via ELISA or LC/MSMS. At 28 days, in placebo-treated patients CSF neurogranin and synaptotagmin concentrations increased 11% and 24% compared to the patient's own baseline values, while in CT1812-treated patients concentrations decreased by 18% and 19%, respectively. The differences between the pooled CT1812 dose groups vs. placebo was significant for neurogranin (p=0.050 ANCOVA) and for synaptotagmin (F_{1,12} = 8.8, p = 0.011, linear mixed model). The reductions in these proteins are

consistent with a positive effect on synapses in Alzheimer's patients and with CT1812's synaptoprotective mechanism of action.

Disclosures: **S.M. Catalano:** A. Employment/Salary (full or part-time);; Cognition Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **N.J. Izzo:** A. Employment/Salary (full or part-time);; Cognition Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **K. Mozzoni:** A. Employment/Salary (full or part-time);; Cognition Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **C. Silky:** A. Employment/Salary (full or part-time);; Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **C. Rehak:** A. Employment/Salary (full or part-time);; Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **M. Grundman:** A. Employment/Salary (full or part-time);; Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.02/M10

Topic: B.06. Synaptic Transmission

Support: NIH Grant AG037337
NIH Grant NS083175
NIH Grant AG047059
NIH Grant AG055247
NIH Grant AG051593
NIH Grant AG054176
ADDF Grant 20100501

Title: Sigma-2 antagonist CT1812 protects synapses from Abeta oligomer-induced loss *in vitro*

Authors: *N. J. IZZO, C. SILKY, C. REHAK, K. MOZZONI, L. WAYBRIGHT, R. YURKO, N. KNEZOVICH, R. MARTONE, S. CATALANO
Cognition Therapeut. Inc., Pittsburgh, PA

Abstract: CT1812 (Elayta™) is a sigma-2 receptor antagonist currently in clinical trials for treatment of Alzheimer's disease (AD). Amyloid-beta oligomers bind to receptors on neurons and cause synaptotoxicity, setting Alzheimer's disease in motion. We hypothesize that when CT1812 binds sigma-2 receptors, the oligomer binding site on the AβO receptor complex is destabilized resulting in an increase in the off-rate of oligomers. CT1812 rapidly displaces bound AβOs from cultured neurons and human Alzheimer's patient brain sections. In living transgenic AD mice (APP/PS1), displaced AβOs can be detected in hippocampal interstitial fluid within 10 minutes of a single dose of CT1812. In cultured brain cells from embryonic rat (DIV21) displacement of AβOs by CT1812 treatment results in restoration of synapse numbers to normal levels within 24 hours as measured by immunofluorescent imaging of the presynaptic marker drebrin. Neurogranin (NRGN) is a postsynaptic calmodulin-binding protein expressed at in neurons in primary hippocampal/cortical cultures. Synaptotagmin-1 (Syt-1) is a presynaptic protein critical for neurotransmission and is expressed in cultured neurons and in synaptic spines. SV2A is a presynaptic vesicle protein that is being explored for monitoring changes in synapses in clinical subjects using PET scans. Treatment of in vitro neurons with Aβ oligomers (24 hrs) cause a 50% loss of NRGN labeled spines, a 35% decrease in SV2A labeled synapses and a 37% loss of synaptotagmin-1 presynaptic terminals (all p<0.01 ANOVA). Treatment of cultures with Aβ in the presence of CT1812 maintained the in vitro labeling of NRGN, Syt-1 and SV2A at between 90% and 95% of control values. These results support the hypothesis that displacement of AβOs from their neuronal receptors will alleviate the synaptotoxicity they induce and restore synapse number to normal. By protecting synapses, CT1812 is a promising disease modifying treatment for AD.

Disclosures: **N.J. Izzo:** A. Employment/Salary (full or part-time); Cognition Therapeutics. **C. Silky:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **C. Rehak:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **K. Mozzoni:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **L. Waybright:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **R. Yurko:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **N. Knezovich:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **R. Martone:** A. Employment/Salary (full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc. **S. Catalano:** A. Employment/Salary

(full or part-time); Cognition Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics, Inc..

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.03/M11

Topic: B.06. Synaptic Transmission

Support: NIH NIGMS grant number 5T32GM077995
Pharmacia predoctoral fellowship
Upjohn Professorship (Brown University)

Title: Differential sigma-2 receptor/TMEM97-mediated cytotoxic and metabolic stimulative properties of monovalent and bivalent SN79 analogs

Authors: *C. Z. LIU¹, B. M. MCVEIGH¹, M. MOTTINELLI², H. E. NICHOLSON¹, C. R. MCCURDY², W. D. BOWEN¹

¹Mol. Pharmacol. and Physiol., Brown Univ., Providence, RI; ²Dept. of Medicinal Chem., Univ. of Florida, Gainesville, FL

Abstract: The sigma-2 receptor was recently identified as TMEM97. Sigma-2 receptor/TMEM97 agonists have traditionally been characterized as ligands that induce programmed cell death in various cell types. Sigma-2 receptor-mediated cell death involves a number of mechanisms including caspase activation, mitochondrial depolarization, and autophagy. Recently, we reported a novel metabolically stimulative function of the sigma-2 receptor, with stimulation of glycolytic hallmarks; effects consistent with a pro-survival function and receptor upregulation in cancer cells. The effects include increased reductive capacity, increase in cellular ATP level, reduction in basal ROS level, and stabilization of HIF-1 α , as determined in human SK-N-SH neuroblastoma cells. Interestingly, both the cytotoxic effect and the metabolic stimulative effect were observed with compounds related to the canonical sigma-2 antagonist, 6-acetyl-3-(4-(4-(4-fluorophenyl)piperazin-1-yl)butyl)benzo[d]oxazol-2(3H)-one (SN79). We have further investigated a series of SN79 analogs in an attempt to assess the structural determinants governing these divergent effects. With focus on the moiety at the 6-position of the benzoxazolone ring, we observed three classes of sigma-2 ligands. CM572, the 6-isothiocyanato derivative (sigma-2 K_i = 14.6 nM), induced cell death in SK-N-SH neuroblastoma cells with EC₅₀ = 7.6 μ M. This ligand also bound irreversibly to the sigma-2 receptor, presumably by attack of the electrophilic isothiocyanate group by a receptor lysine or cysteine residue in the binding site. CM571, the 6-amino derivative (sigma-2 K_i = 21.7 nM), caused a dose-dependent stimulation of MTT reduction, indicating the metabolic stimulative-effect,

producing 40% stimulation at 30 μ M. MAM03055A (MAM) is a thiourea-linked dimer of the amine, CM571. MAM exhibited high affinity for sigma-2 receptors ($K_i = 56.7$ nM) and like CM572, induced dose-dependent cell death in human SK-N-SH neuroblastoma cells, with an $EC_{50} = 9.24$ μ M. The parent compound, SN79, with a 6-methylketone moiety (sigma-2 $K_i = 6.89$ nM), is “neutral”, i.e., neither cytotoxic nor metabolic stimulative. Thus ligands in this structural platform fall into three classes: neutral, cytotoxic, and metabolic stimulative. Compared with the three monovalent ligands, it is surprising that MAM behaves like CM572 and not like CM571, which comprises its monomer. Sigma-2 receptor covalent binding cannot account for the similarity, since MAM lacks ability to react with a receptor nucleophile. These results suggest that monovalent and bivalent sigma-2 ligands have unique modes of receptor interaction that deserve further study.

Disclosures: C.Z. Liu: None. B.M. McVeigh: None. M. Mottinelli: None. H.E. Nicholson: None. C.R. McCurdy: None. W.D. Bowen: None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.04/M12

Topic: B.06. Synaptic Transmission

Support: Robert A. Welch Foundation (F-0652)

NIH AA024439

NIH AA020992

Title: Small molecule modulators of Sig2R/Tmem97 reduce alcohol withdrawal-induced behaviors

Authors: *S. MARTIN¹, L. SCOTT², J. SAHN¹, A. FERRAGUD³, J. PIERCE², V. SABINO³
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Abstract: Repeated cycles of intoxication and withdrawal enhance the negative reinforcing properties of alcohol and lead to neuroadaptations that underlie withdrawal symptoms driving alcohol dependence. Pharmacotherapies that target these neuroadaptations may help break the cycle of dependence. The sigma-1 receptor (σ_1R) subtype has attracted interest as a possible modulator of the rewarding and reinforcing effects of alcohol. However, whether the sigma-2 receptor, which we recently cloned and identified as transmembrane protein 97 ($\sigma_2R/TMEM97$), plays a role in alcohol-related behaviors is currently unknown. Using a *Caenorhabditis elegans* model, we identified two novel, selective $\sigma_2R/Tmem97$ modulators that reduce alcohol withdrawal behavior via an ortholog of $\sigma_2R/TMEM97$ and dependent on PGRMC1. We then

show that one of these compounds reduced withdrawal-induced excessive alcohol drinking in a well-established rodent model of alcohol dependence. These key discoveries provide the first evidence that $\sigma 2R/TMEM97$ is involved in alcohol withdrawal behaviors and that this receptor is a potential new target for treating alcohol use disorder.

Disclosures: **S. Martin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co Founder NuvoNuro, Inventor on patent applications. **L. Scott:** None. **J. Sahn:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co Founder NuvoNuro, Inventor on patent applications. **A. Ferragud:** None. **J. Pierce:** None. **V. Sabino:** None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.05/M13

Topic: B.06. Synaptic Transmission

Support: NIH Grant AG027956

Title: Let7i as a key regulator of Pgrmc1 and progesterone-induced neuroprotection

Authors: *M. SINGH¹, T. NGUYEN¹, C. SU²

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Abstract: Progesterone (P4) is a potent neuroprotectant and a promising therapeutic for stroke treatment. However, the underlying mechanism(s) remain unclear. One known mediator of P4's protective effects is brain-derived-neurotrophic-factor (BDNF). Of note, we recently reported that P4 induces a significant release of BDNF from primary astrocytes, an effect that required the expression of progesterone-receptor-membrane-component-1 (Pgrmc1). Pgrmc1 is abundantly expressed in the brain and mediates various beneficial effects of P4 including anti-apoptosis, spinogenesis, and BDNF release. What is not known, however, is how the expression of this receptor is regulated. Our in silico analysis revealed that Pgrmc1 is a putative target of the microRNA, let-7i. Based on this, we hypothesized that let-7i represses P4's neuroprotective effects by down-regulating the expression of Pgrmc1, and that inhibition of let-7i could facilitate progesterone-induced neuroprotection. Using the middle cerebral artery occlusion (MCAo) model of stroke, applied to ovariectomized mice, we evaluated if a let-7i inhibitor, delivered via intracerebroventricular (ICV) injection, would enhance the neuroprotective effects of progesterone and facilitate functional recovery beyond that elicited by progesterone alone. Our results demonstrate that let-7i increases as a function of ischemic injury (e.g., stroke), and that overexpression of let-7i negatively regulates Pgrmc1 expression, disrupts P4-induced BDNF

release and reduces P4's cytoprotective effects. Inhibition of let-7i expression (using an antagomir), however, enhanced P4-induced neuroprotection and facilitated functional recovery in the MCAo model of stroke in a manner that was far superior to the effect of P4 alone. Collectively, our data suggest that an elevated expression of let-7i negatively influences P4-induced neuroprotection through the regulation of the Pgrmc1/BDNF axis, and supports the use of a let-7i antagomir to enhance the neuroprotective effects of progesterone.

Disclosures: **M. Singh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent filed on technology associated with the research. **T. Nguyen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent filed on technology associated with the research. **C. Su:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent filed on technology associated with the research.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.06/M14

Topic: B.06. Synaptic Transmission

Support: NIH R01 AG052550

P01 AG03991

P50 AG05681

Title: Sigma-1 and sigma-2 receptor densities do not correlate with tau pathology in the frontal cortex of AD brains

Authors: ***J. XU**¹, **Y. GUO**², **N. J. CAIRNS**³, **J. C. MORRIS**⁴, **T. BENZINGER**⁴

¹Radiology, ³Neurol., ²Washington Univ. Sch. of Med., Saint Louis, MO; ⁴Washington Univ., St. Louis, MO

Abstract: *N*-[4-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-yl)butyl]-2-methoxy-5-methylbenzamide (**RHM-1**), a conformationally-flexible benzamide analogue, has been shown to have high affinity and selectivity for sigma-2 receptor versus sigma-1 receptor and the dopamine D₂ and D₃ receptors (*Bioorg. Med. Chem. Lett.* **2004**: 14; 195-202, *Eur. J. Pharmacol.* **2005**; 525: 8-17). Its high sigma-2 receptor affinity (K_i <10 nM) and selectivity (sigma-1: sigma-2 ratio > 300) indicates that it may be a useful radioligand to assess the sigma-2 receptors in the brain.

Therefore, **RHM-1** was radiolabeled with tritium (specific activity = 80 Ci/mmol) and the binding of [³H]**RHM-1** to sigma-2 receptors of aged human postmortem brain tissue was

evaluated in vitro using quantitative autoradiography. The sigma-1 and sigma-2 receptors were found to be extensively distributed in different brain regions, sigma-2 density is about two-fold higher than sigma-1 receptor density in most brain regions: frontal cortex, precommissural caudate and putamen, postcommissural caudate and putamen, nucleus accumbens, globus pallidus, thalamus and substantia nigra; in the red nucleus, sigma-1 and sigma-2 densities are equal. The high binding density of sigma-2 receptor in the aged brains suggests that sigma-2 receptor may play an important role in the brain disorders such as Alzheimer diseases (AD). In this study, we compared sigma-1 and sigma-2 receptor densities with Tau density measured using a selective Tau radioligand [³H]MK6240 in the frontal cortexes of 7 aged AD brains (6 females and 1 male, age range: 74 to 88 years, Tau tangle rating: 4 to 6). No obvious correlation was found between sigma-1 and sigma-2 receptor and Tau binding densities.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.07/M15

Topic: B.06. Synaptic Transmission

Title: Therapeutic and diagnostic targeting of sigma-2 receptors in oncological and neurodegenerative diseases

Authors: *F. SPINELLI¹, M. PATI¹, E. FANIZZA^{2,3}, N. COLABUFO¹, N. DENORA¹, N. DEPALO³, C. ABATE¹

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Abstract: The well-established role of sigma-2 receptor in cancer triggers the development of molecules as suitable tools for studying the involvement of this receptor in physiological and pathological conditions through imaging techniques. In particular, sigma-2 receptor results abundantly overexpressed (\approx 10-fold) in proliferating tumor cells rather than in quiescent tumor cells, and its activation has been also associated with tumor cell death. Therefore, sigma-2 receptor emerges as an interesting target for diagnostic and therapeutic purposes in cancer. In the last years we focused our research on the design and synthesis of fluorescent probes useful for better studying the sigma-2 receptor pathways through fluorescent imaging. Here we report the development of innovative fluorescent nanostructures for sigma-2 receptor as tumor imaging probes and potential therapeutic agents. These nanostructures have been prepared conjugating two specific sigma-2 receptor ligands (i.e. MLP66 and TA6) with luminescent semiconductor quantum dots coated with a hydrophilic silica shell (QD@SiO₂). QDs have been selected as

fluorescent agents thanks to their superior optical properties, high resistance to photobleaching, long fluorescence lifetime, and good solubility in aqueous buffer. QD@SiO₂-MLP66 and QD@SiO₂-TA6 have been tested in flow cytometry and confocal fluorescence microscopy experiments on cancerous MCF7 cells, which constitutively overexpress the sigma-2 receptor. This in vitro evaluation showed the ability of the before mentioned fluorescent nanoprobe to be internalized in the cells in a time-dependent manner and to bind selectively the sigma-2 receptors abundantly expressed in the cytoplasm. These preliminary results suggest that the proposed functionalized nanostructures can be selectively delivered to the sigma-2 receptor overexpressed in tumor cells, representing a very interesting promise in the oncology field not only for diagnostic but also for therapeutic purposes. Indeed, these nanostructures can exert tumor specific cytotoxic effects through the targeted delivery of drug payloads to sigma-2 receptor overexpressing tumor cells. Beyond the role of sigma-2 proteins in cancer, increasing number of evidence has suggested an important role of sigma-2 receptor also in neurodegenerative diseases and the luminescent nanoprobe here described could surely provide deeper insights in this regard.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.08/M16

Topic: B.06. Synaptic Transmission

Title: The essential role of sigma-2 receptor/TMEM97 and progesterone receptor membrane component 1 in the internalization of low-density lipoprotein via an interaction with the low-density lipoprotein receptor

Authors: ***A. RIAD**, C. ZENG, C.-C. WENG, S. CARLIN, R. H. MACH
Radiology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Background: The Sigma-2 Receptor/Transmembrane Protein 97 (TMEM97) and Progesterone Receptor Membrane Component 1 (PGRMC1) have both been implicated in cholesterol homeostasis in cells. TMEM97 and PGRMC1 are widely expressed in the nervous system and regulate signaling pathways that are important to neurodegenerative diseases. Their involvement in trafficking, with cholesterol homeostasis pathways, and their presence on membranes may indicate an involvement with the Low-Density Lipoprotein Receptor (LDLR) to facilitate the internalization and uptake of Low-Density Lipoprotein (LDL).

Hypothesis: We hypothesize that the presence and interaction of both TMEM97 and PGRMC1 with LDLR are important for the uptake of LDL via the formation of a complex with LDLR that

facilitates successful internalization of the lipoprotein.

Methods: To study these receptors we utilized HeLa cells as a model system and used CRISPR/Cas9 to generate TMEM97 knockout, PGRMC1 knockout, and TMEM97/PGRMC1 double knockout (DKO) cell lines. This model system was used to assess the effect that these receptors have on the uptake of LDL radiolabeled with [³H]cholesterol. We also assessed the uptake of fluorescently labeled DiI-LDL and examined the localization of these proteins during LDL uptake.

Results: Our results indicate that the ablation of one or both of the receptors result in similar inhibition of LDL uptake, suggesting that the presence of both TMEM97 and PGRMC1 are necessary for the internalization of LDL-LDLR complex. Interestingly, the knockout cells did not show a reduction of LDLR levels, nor a reduction in its capacity to bind LDL, suggesting that TMEM97 and PGRMC1 are involved in the internalization process. Further, treating control cells with a TMEM97 ligand resulted in decreased LDL uptake at levels similar to the knockout cell lines. Immunofluorescence studies indicated that PGRMC1 and LDLR colocalize on the plasma membrane, and upon treatment with LDL, TMEM97 becomes associated with the complex.

Conclusion: TMEM97 and PGRMC1 are involved in the internalization of LDL by interacting with the LDLR upon LDL binding. The interaction of all three components — LDLR, TMEM97, and PGRMC1 — are necessary for lipoprotein uptake as demonstrated by their similar capacity to bind LDL, yet diminished ability to internalize it. Moreover the DKO cell line shows comparable reductions in internalization as each of the single knockout cell lines, taken together with the microscopy colocalization this suggests the formation of a quaternary protein complex, where all three receptors along with bound LDL are required for internalization.

Disclosures: **A. Riad:** None. **C. Zeng:** None. **C. Weng:** None. **S. Carlin:** None. **R.H. Mach:** None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.09/M17

Topic: B.06. Synaptic Transmission

Support: Department of Radiology at University of Pennsylvania, Perelman School of Medicine

Title: Biological roles of TMEM97 and PGRMC1 in cell growth and sigma-2 ligand-induced cell death

Authors: ***C. ZENG**, H. WINTERS, C.-C. WENG, L. PUENTES, M. SCHNEIDER, C. RAQUEL, K. XU, M. MAKVANDI, R. MACH
Radiology Dept., Univ. of Pennsylvania Perelman Sch. of Medi, Philadelphia, PA

Abstract: Sigma-2 receptors have been implicated in tumor proliferation and neurodegenerative diseases. Progesterone receptor membrane component 1 (PGRMC1) was previously reported as a putative sigma-2 receptor but subsequent evidence disproved this result. Recently sigma-2 receptors have been identified as transmembrane protein 97 (TMEM97). In the current study, we studied biological roles of TMEM97 and PGRMC1 in cell growth and sigma-2 ligand-induced cell death using Hela cells as a model. We also looked for functional relationship between TMEM97 and PGRMC1. We have knocked out TMEM97, PGRMC1, and both TMEM97 and PGRMC1 in Hela cells using CRISPR technology, and the knockout was confirmed by real time PCR and western blot analysis. Western blot data showed that TMEM97 knockout did not affect PGRMC1 protein levels and vice versa. Cell growth curve data showed that doubling times for control, TMEM97 knockout (KO), PGRMC1 KO, and TMEM97 & PGRMC1 double KO cell lines were 27, 31, 25, and 27 hours, respectively, suggesting that TMEM97 may increase growth rate whereas PGRMC1 may inhibit growth rate. Sigma-2 ligands with various structures have been shown to induce cell death in cancer cells. Viability assay and caspase 3 assay were performed in control, TMEM97 KO, PGRMC1 KO, and TMEM97 & PGRMC1 double KO cell lines treated with various sigma-2 ligands. The data showed that TMEM97 knockout did not affect the concentrations of sigma-2 ligands that give half-maximal responses (EC_{50}), suggesting that cytotoxic effects of sigma-2 ligands may not be mediated by TMEM97. On the other hand, PGRMC1 knockout decreased EC_{50} , suggesting that PGRMC1 may make cells more resistant to sigma-2 ligand-induced cytotoxicity. Understanding biological roles of TMEM97 and PGRMC1 will facilitate development of sigma-2 ligands as drugs for treatment of cancer and neurodegenerative diseases.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.10/M18

Topic: C.01. Brain Wellness and Aging

Title: Identification of a second [3H]DTG binding site on TMEM97-KO cell membranes

Authors: *C.-C. WENG¹, C. ZENG², A. RIAD¹, K. XU¹, R. H. MACH¹

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Abstract: Purpose The Sigma-2 Receptor (S2R) has been proposed as being a promising tumor proliferation marker and a possible tumor therapeutic target for decades. Recent studies have indicated it as a novel target for treating Alzheimer's disease. A recent study reported

Transmembrane Protein 97 (TMEM97) as the S2R. In the present study, we report a low affinity binding target for [³H]DTG on TMEM97 knockout (KO) cells that suggest the existence of a novel receptor having sigma receptor pharmacology. **Materials and methods** TMEM97-KO, Progesterone Receptor Membrane Component 1 (PGRMC1) KO, and TMEM97/PGRMC1 double knockout (DKO) cell lines were prepared utilizing CRISPR/Cas9 on human HeLa cells. For S2R saturation binding assays [³H]DTG (2 - 400 nM) was used; nonspecific binding was defined with unlabeled DTG (40 μM). To block binding of DTG to S1R, 5 μM of PRE-084 was added. [¹²⁵I]RHM-4 (0.03-6 nM) was also used for S2R binding assays, with 10μM DTG to define nonspecific binding. For S1R saturation binding assays, [³H]Pentazocine (0.5-80 nM) was used in the absence and presence of 10 μM haloperidol to define nonspecific binding. All assays were performed for 90 min at room temperature. K_d and B_{max} values for these assays were calculated from a nonlinear regression method using Prism. **Results** No significant differences were observed for [³H]Pentazocine binding on S1R (B_{max}~3000 fmol/mg) in the three KO cell lines versus control HeLa cells. The saturation binding results of [³H]DTG and [¹²⁵I]RHM-4 on control HeLa cell membranes (Scramble/Cas9 HeLa cell line) and PGRMC1-KO cell membranes were different (B_{max}~3000 fmol/mg for [³H]DTG, B_{max}~2000 fmol/mg for [¹²⁵I]RHM-4). No specific binding was observed for [¹²⁵I]RHM-4 on the TMEM97-KO and TMEM97/PGRMC1-KO cell membranes; however, when these two membranes were treated with [³H]DTG, a low affinity residual binding site was detected (K_d values were 260-300nM, B_{max} values were 800-1000 fmol/mg). **Conclusions** CRISPR/Cas9 knockout of TMEM97 eliminated nearly all the specific binding of [¹²⁵I]RHM-4, but reduced [³H]DTG binding roughly by 80%. The data presented herein suggests the existence of a low affinity binding site that displays sigma receptor pharmacology.

Disclosures: C. Weng: None. C. Zeng: None. A. Riad: None. K. Xu: None. R.H. Mach: None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.11/N1

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

Support: NIH Grant EY022358

Prevent Blindness Fellowship for Female Scholars in Vision Research

Title: CD36-dependent amyloid pathology in the retinal projection

Authors: *E. S. PLYLER¹, M. A. SMITH¹, J. R. RICHARDSON², C. M. DENGLER-CRISH², S. D. CRISH²

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Abstract: Chronic neurodegenerative diseases such as Alzheimer's disease (AD) and glaucoma share many pathophysiological similarities. AD-associated neurotoxic proteins, including amyloid-beta ($A\beta$), have been identified in post-mortem ocular tissues from AD patients as well as in animal models of AD, glaucoma, age-related macular degeneration, and diabetic retinopathy. Intriguingly, $A\beta$ deposits are detected in the retina of AD patients prior to detection in the brain, making it an attractive target for early detection and therapeutic intervention. However, the mechanisms by which $A\beta$ accumulates, spreads, and promotes cellular degeneration remain unclear.

Neuroinflammation plays an important role in spreading and exacerbating pathology in many chronic age-related neurodegenerative diseases, including glaucoma and AD. Microglia, the primary immune cell of the central nervous system, recognize and bind $A\beta$ through a number of membrane receptors including scavenger receptor B3, AKA cluster of differentiation 36 (CD36). Activation of the CD36 receptor induces an intracellular signaling cascade that promotes secretion of pro-inflammatory cytokines and production of reactive oxygen species (ROS). Thus, CD36 receptor activation by $A\beta$ may serve as a mechanism of initiating a pro-inflammatory environment that propagates and exacerbates amyloid pathology through the retinal projection. We found that CD36 colocalizes with microglia in the retina and its brain targets in young, pre-glaucomatous DBA/2J mice, but is primarily associated with retinal vasculature in aged DBA/2J mice exhibiting glaucomatous pathology. We also report that an intravitreal injection of fibrillized amyloid-beta (1-42) produces extensive gliosis and neurodegeneration in the retina and its brain targets within 2 weeks. Interestingly, CD36-null mice are resistant to this amyloid-induced retinal pathology. This indicates not only that CD36 is needed for $A\beta$ -mediated retinal pathology, but also suggests that age and/or pathology-related vascular changes associated with CD36 may play a role in tissue vulnerability in chronic neurodegenerations.

Disclosures: **E.S. Plyler:** None. **M.A. Smith:** None. **J.R. Richardson:** None. **C.M. Dengler-Crish:** None. **S.D. Crish:** None.

Poster

045. Alzheimer's Disease and Other Dementias: A β Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.12/N2

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

Title: Sex differences in pathology of the visual system in the 3xtg mouse model of Alzheimer's disease

Authors: ***G. FRAME**¹, **M. A. SMITH**², **J. K. LEPP**², **L. LIN**², **E. S. PLYLER**², **P. GATES**¹, **Z. B. SLUZALA**³, **S. D. CRISH**², **C. M. DENGLER-CRISH**²

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Abstract: Amyloid-beta (A β)— one of the major pathological proteins in Alzheimer’s disease (AD), accumulates in the retina and seems to emerge before appearance of brain pathology. Retinal amyloid is visible *in vivo*, making it a potentially useful, early biomarker of the disease. Retinal A β is shown to have deleterious effects on retinal ganglion cells (RGC), and likely influences visual deficits that frequently emerge in the earliest stages of AD. Early evidence of retinal amyloid has been characterized in several transgenic AD mice models, including the popular 3xtg-AD mouse. However, the effects of retinal A β on the rest of the anterior visual system remain to be determined. Here, we characterized the time course of amyloid emergence in the retina and superior colliculus (SC), the major retinal projection target in mice, and determined its impact on visual behavior.

We found increased amyloid load in retina and SC of female 3xtg mice that began as early as 2 months of age. At 6 months of age, 3xtg oculomotor response (OMR) indicated reduced visual acuity compared to C57BL6J (C57) controls, and by 12 months, 50% of 3xtg mice tested failed to demonstrate any OMR. When contrasted with males, female 3xtg exhibited greater severity of deficits at earlier ages; however male 3xtg demonstrated visual system defects as well.

Additionally, we found that anterograde axon transport from the eye to the brain was deficient in female 3xtg by 7 months of age, followed by indicators of RGC axon terminal, but not axon, loss in our 12-14 month age group. Transport deficits and terminal loss were not seen in male 3xtg mice at these ages.

These changes parallel the pattern of pathology seen in glaucoma, an optic neuropathy often comorbid with AD. Glaucoma is characterized by elevated intraocular pressure (IOP) driving RGC degeneration; therefore, we measured IOP in 3xtg mice across age to determine if elevated IOP could explain visual system pathology. We saw significant sex differences in 3xtg IOP across age. In young (3 mo.) female 3xtg, IOP was significantly lower than C57 females, and increased to control levels by 12 mo. In 3mo. male 3xtg, IOP was comparable to male C57 mice, but decreased significantly by 7 mo. While IOP for all mice fell within “normal” non-glaucomatous range, these group differences in magnitude were large effects.

Our findings indicate that A β may have deleterious effects throughout the anterior visual system and underscore the importance of assessing sex differences in neurodegenerative models.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.13/N3

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

Support: Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (Faperj)
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
Human Frontiers Science Program (HFSP)
Instituto Nacional de Neurociência Translacional (INNT)

Title: Activation of interleukin-6 signaling pathway in the hippocampus of rodent models of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is the most prevalent type of dementia affecting the elderly population. Cumulative evidence pose neuroinflammation as a central player of memory loss observed in AD. Cytokines, like the interleukine-6 (IL6), are components of the pro-inflammatory response in the brain involved with several injuries and diseases. Data from the literature indicates that IL6 are upregulated in AD and might be involved with memory decline, but further studies focusing on the association between IL6 and AD are warranted. IL6 signaling pathway involves the phosphorylation of signal transducer and activator of transcription 3 (pSTAT3), which mediates the expression of suppressor of cytokine signaling 3 (SOCS3). In the present work we analyzed the effect of A β oligomers, toxins that accumulate in the brains of AD patients, in hippocampal IL6-STAT3-SOCS3 pathway. Rat primary hippocampal cultures were maintained for 21 days *in vitro* and treated with A β Os (500nM) for 24 hours. C57bl/6 male mice were intracerebroventricularly (i.c.v.) injected with 100pmol of A β Os and their hippocampus were extracted 24 hours later. The hippocampus of 11-month-old APP/PS1 male mice were also analyzed. Cultures treated with A β Os presented increased levels of IL6 in the culture media and pSTAT3 in the protein extracts when compared to cultures treated with vehicle. The hippocampus of wild-type (WT) mice that received the A β Os presented enhanced expression of IL6 and SOCS3. A β O-injected and APP/PS1 mice presented elevated protein levels of pSTAT3. Collectively, these results indicate that IL6 signaling pathway might be over-activated and involved with AD pathogenesis.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.14/N4

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

Support: NIH Grant P50AG047270

Alzheimer's Association Research Fellowship AARF-17-504924

Title: Relationship between amyloid- β plaques and cortical parvalbumin-positive interneurons in 5xFAD mice

Authors: S. BARINGER, F. ALI, *A. C. KWAN
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Abstract: Alzheimer's disease (AD) is characterized by widespread accumulation of neurofibrillary tangles and amyloid- β plaques, including in the cortex. While these are associated with death in the general population of neurons, how they affect specific classes of cortical neurons is unclear. Here, we studied the relationship between parvalbumin-positive (PV) neurons, an important GABAergic interneuron class, and amyloid- β plaques in 5xFAD mice with mutations in APP and PSEN1 genes associated with familial AD in humans. We used immunohistochemistry to stain for PV neurons in four different regions of the neocortex - prelimbic (PrL), anterior cingulate (Cg), secondary motor (M2) and primary somatosensory (S1) cortices - as well as amyloid- β plaques (using FSB). First, we found a higher plaque burden (size and density of amyloid- β plaques) in association cortices (PrL, Cg and M2) compared to S1. There was also reduced density of PV interneurons in 5xFAD mice relative to wild-type (WT) in the deep layers (layers 5 and 6) of association cortices but not in the superficial layers (layers 2 and 3). The loss of PV interneurons was particularly pronounced in Cg (~50% reduction). We further examined the relationship in spatial distribution of amyloid- β plaques and PV interneurons. We found in Cg, but not in the other areas, that there tended to a higher density of plaques near PV interneurons (within ~30 micrometers) and that these plaques tended to be larger than plaques farther away, indicating a possible relationship between PV interneuron activity locally and amyloid- β plaque growth. Overall, our results suggest some regional heterogeneity, implicating the Cg as especially vulnerable to amyloid- β pathology and growth. We are following up these results with causal manipulations and in vivo two-photon imaging to further elucidate the relationship between PV interneurons and amyloid- β plaques.

Disclosures: S. Baringer: None. F. Ali: None. A.C. Kwan: None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.15/N5

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

Support: HR14C0002
NRF-2015M3A9E2028884

Title: *In vivo* evaluation of amyloid and tau pathology in the novel 6xFAD mouse model of Alzheimer's disease

Authors: *S. KANG¹, M. BAEK², E. NAM¹, H. PARK³, Y.-H. SUH², K.-A. CHANG^{1,2,3}
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Abstract: Objectives : Alzheimer's disease (AD), the most common dementia, is characterized by the deposition of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). To understand the pathological mechanism of AD, various mouse models have been developed. One of them is 5xFAD mouse which has three mutations of human APP genes(KM670/671NL, I716V, and V717I) and two mutations of human PS1(M146L and L286V). These mice show amyloidopathy and cognitive impairment in early stage. However, the NFTs is invisible in 5xFAD

Methods : In the present study, we developed a novel AD mouse model mouse (6xFAD) through crossbreeding the 5xFAD mouse with Tg2508 mouse expressing mutant tau protein (P301L). To evaluate the neuropathology of these mice, we performed cognitive behavior test. We conducted histopathological experiments, western blot, and micro positron emission tomography (PET) imaging analysis to examine AD hallmarks as A β and p-tau. PET studies were performed with amyloid PET radiotracer, [18F]flutemetamol and tau PET radiotracer, [18F]THK5351.

Additionally, A β was administered to the unilateral hippocampus (AP, -1.4 mm; ML, 1.3 mm; DV, -1.9 mm) to observe the effect of A β on tau pathology.

Results : In behavior test, when 6xFAD was compared with 5xFAD, cognitive impairment significantly increased. We showed that formation of the early stage amyloid plaque, tau pathology and neuronal loss by histopathological experiments in 6xFAD compared with 5xFAD and Tg2508. Both radiotracer PET probes showed higher density in 6xFAD than 5xFAD and Tg2508. An age-dependent amyloid- and tau-pathology detection of 6xFAD correlated with histochemical results. Additionally, tau was phosphorylated by infusing A β to mice. This shows that A β is involved in the phosphorylation of tau.

Conclusions : 6xFAD expressed memory loss and AD hallmarks as A β , phosphorylated tau in

earlier stage than 5xFAD. Therefore, our results suggest that these novel 6XFAD mice (5XFAD x Tg2508) might be advanced animal models to study of Alzheimer's disease.

Disclosures: S. Kang: None. M. Baek: None. E. Nam: None. H. Park: None. Y. Suh: None. K. Chang: None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.16/N6

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

Support: NIH Grant AG052934
NIH Grant AG028488
University of Michigan – Protein Folding Disease Initiative

Title: Does acarbose treatment differentially affect physiological or pathological mechanisms in the 5xFAD mouse model of Alzheimer's disease over the lifespan?

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Abstract: Deficits in cognitive function, especially in the ability to learn and remember new information, is a characteristic of many neurodegenerative diseases, including Alzheimer's disease (AD). These impairments progressively and irrevocably worsen, severely impacting an individual's ability to function independently in daily life. Importantly, advancing age remains the single largest risk factor for developing AD, and as the aged population continues to expand, AD-related dementia is likely to further escalate as a health concern for affected individuals and as a burden on the healthcare system. The National Institute on Aging's Interventions Testing Program seeks to identify treatments that can extend lifespan, and because of the tight link between aging and the development of AD, interventions that successfully slow the aging process represent potential therapeutic interventions that may ameliorate deficits associated with age-related diseases like AD. One drug, acarbose (Aca), that has been shown to significantly extend lifespan in a genetically heterogeneous mouse line (UM-HET3), is of particular interest because it is already used in the treatment of diabetes and is known to be safe and well-tolerated in humans; thus, it has the potential for rapid translation into clinical studies. Our preliminary behavioral studies suggest that Aca improves learning and memory performance over the lifespan in wild-type (WT) mice but appears only to improve performance in the 5XFAD mice at

the earliest stages of disease onset. We now interrogate the cellular and molecular mechanisms that may underlie the differential effect of Aca on age-related versus disease-related deficits in cognitive performance. In particular, we will test whether specific pathological features of AD (including the deposition of A β plaques and Tau tangles) are altered between 5xFAD mice on a normal or Aca diet, as well as whether more general features (such as the inflammatory response) are altered between WT and 5xFAD mice receiving the Aca diet. Taken together, these new studies will elucidate the mechanisms engaged by Aca treatment to serve as a therapeutic intervention aimed at ameliorating cognitive decline in the aging population and in those affected by neurodegenerative disease.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.17/N7

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

Title: Mutagenic analysis of inhibitory and facilitatory modulation of $\alpha 7$ nAChRs by A β (1-42)

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Abstract: Alpha 7 ($\alpha 7$) nicotinic acetylcholine (ACh) receptors (nAChRs; Rs) are distributed throughout the brain, particularly in areas involved in learning and memory. They are abundant in the cholinergic projections from the basal forebrain to the hippocampus that deteriorate early in Alzheimer's disease (AD). Several studies (including our own) have found that high (nM - μ M) concentrations of amyloid beta (A β) peptides inhibit $\alpha 7$ R activity (e.g., Wu et al., 2004; Pym et al., 2005). In contrast, recent studies suggest that picomolar concentrations interact with $\alpha 7$ Rs in a facilitatory way, suggesting potentially positive roles for A β in certain learning- and memory-related processes (Puzzo et al., 2008). Previous work in our lab has shown that 100 pM A β (1-42) increased peak amplitudes and slowed desensitization of ACh-evoked $\alpha 7$ R currents, expressed in *Xenopus* oocytes, similar to but less strongly than the type II positive allosteric modulator (PAM) PNU 120596. PNU 120596 (but not the type I PAM, genistein) also occluded the effects of 100 pM A β (1-42). 100 pM A β (1-42) was never observed to directly activate $\alpha 7$ Rs. To further explore A β 's PAM-like interaction with $\alpha 7$ Rs, we developed the M276L mutation demonstrated to suppress potentiation of $\alpha 7$ Rs by type II PAMs (Young et al., 2008). Facilitation of peak and total ACh-evoked currents by 100 pM A β (1-42) was abolished in the

M276L $\alpha 7$ Rs, as was the slowing of desensitization, and the PNU 120596-facilitation was greatly reduced (56% reduction), providing additional evidence that 100 pM A β (1-42) acts as a type II PAM. Surprisingly, higher concentrations of A β (1-42) [100 and 500 nM] that partially inhibited ACh-evoked currents through wt $\alpha 7$ Rs failed to inhibit M276L $\alpha 7$ Rs. Instead, moderate but non-significant facilitations of peak and total currents (~41% and ~34% increase, respectively, for 500 nM) were observed, as was a small (~6%) slowing of desensitization. These results suggest that modulation of wt $\alpha 7$ R activity by both inhibitory and facilitatory A β (1-42) concentrations relies on the M276 residue and, therefore, occur via the same/overlapping (rather than distinct) binding site. We suggest that the PAM actions of 500 nM A β (1-42) on mutant $\alpha 7$ Rs are functionally equivalent to those of 100 pM on wt $\alpha 7$ Rs, because of reduced binding site affinity of the mutant for the principal tertiary species of A β peptide that interacts with the M276L residue. High A β (1-42) concentrations (500 nM) may contain enough of the critical tertiary species to bind to the M276L site and potentiate $\alpha 7$ R activity. For high-affinity wt $\alpha 7$ Rs, other tertiary A β peptide(s) present within high (500 nM) concentrations may inhibit the channel.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.18/N8

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

Support: FAPESP
CNPQ
CAPES

Title: Exercise associated with mesenchymal stem cell transplantation decrease anti-inflammatory cytokines in Alzheimer's disease mice model

Authors: ***D. HASHIGUCHI**¹, D. Y. HUKUDA¹, H. C. CAMPOS^{1,2}, S. G. SILVA^{2,3}, A. COPPI⁴, R. ARIDA¹, B. M. LONGO¹

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Abstract: Background: Alzheimer's disease (AD) is a neurodegenerative disorder and its main neuropathological features are the accumulation of neurofibrillary tangles and amyloid plaques with an inflammatory component. Considering the absence of an effective treatment, physical

activity has emerged as an alternative treatment to retard the progression of AD. Studies propose physical exercise as a neuroprotective factor against Alzheimer disease but little is known about how resistance exercise, which is highly recommended for aging people, interfere on inflammatory response related to neurodegeneration in AD. Mesenchymal stem cells (MSCs) are involved in the mechanisms of immunoregulation, trophic and antiapoptotic actions, as well as to promote angiogenesis and vasculogenesis. Based on the above mentioned evidence, we hypothesized that MSC hippocampal transplantation associated with a resistance exercise program would interfere with inflammatory response of transgenic mice for AD. **Methods:** Double transgenic 6-7 month-old male mice APP/PS1 were used as Alzheimer's disease model, and the respective wild type mice (WT) as controls. The mice were divided into eight groups (n=15 each one): AD group (AD); AD submitted to MSC transplantation (AD+MSC); AD submitted to exercise program (AD+EX); AD transplanted with MSC and submitted to exercise (AD+MSC+EX); Wild Type group (WT); WT MSC transplanted (WT+MSC); WT submitted to exercise (WT+EX); WT MSC transplanted and submitted to exercise (AD+MSC+EX). The resistance exercise protocol consisted of eight climbing series with a progressively heavier load during 4 weeks. At the end of the 4th week of exercise, animals were euthanized by decapitation or perfusion. Fresh hippocampal samples were collected to quantify the expression of IL-1 α , IL-6, IL-4, IL-10 analyzed by ELISA, and the perfused material (hippocampus) were cryostat cut (40 μ m) and processed by immunohistochemistry for Iba-1 microglial marker, quantified by stereology in the hippocampus. **Results:** MSC transplanted into the hippocampus of AD animals submitted to resistance exercise reduced the hippocampal levels of pro inflammatory cytokines such as IL-1 α and IL-6, and the transplantation increased the level of IL-4 anti inflammatory cytokine. However no changes were found in IL-10 anti inflammatory cytokine. **Conclusions:** These immunomodulatory mechanisms of MSC, together with a physical activity program of resistance exercises, bring strong therapeutic implications for the AD, which is essential in understanding the triggering mechanisms of neurodegenerative processes of the disease.

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Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.19/N9

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

Support: R01 MH109466

Title: Are there sex differences in the tta:apsi mouse model of Alzheimer's disease after chronic unpredictable stress?

Authors: *M. PALUMBO¹, H. DONG²

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and females make up 70% of the AD population. Although previous studies have suggested the risk factors for developing AD include genetics, age and hormones, little is known about the sex-dependent pathways that may induce female vulnerability to AD. Recent studies have shown chronic stress exacerbates the onset and disease progression. Previous work in animal models of AD, such as APPS1 and Tg2576, exposed to persistent stress show increased soluble A β and A β plaques, neuronal dysfunction, apoptosis, and accelerated learning and memory impairments. However, these models show baseline sex differences in APP expression, thus are not ideal models to investigate sex-differences in AD pathology. Studies indicate the tTA:APPsi mouse model of AD shows no intrinsic sex-differences in APP expression or cognitive deficits. Thus, in this study we use the tTA:APPsi mouse to assess the effects of chronic unpredictable stress (CUS) on the behavior and neuropathogenesis of AD, and if such changes display in a sex-dependent manner. In order to characterize the developmental progression of AD, animals are divided into age groups of 4 and 7 months, with equal numbers of males, females and corresponding WT littermates (N=8 per group). Stressed groups will be exposed to CUS for 4 weeks then tested for learning, memory, anxiety and depressive-like behavior. Control animals of the same age were not exposed to stress, but still performed behavioral assays. Animals will then be used for biochemical analysis of A β oligomers, A β -40, A β -42, APP expression, A β plaques, and corticosterone levels. Our preliminary data on stressed 4-month-old animals demonstrated decreased locomotor activity in the open field, immobility in the forced swim test, and increased arm entries in the Y-Maze test compared to unstressed mice. However, we have not found significant differences in behavior between tTA:APPsi and WT mice, or between sexes. Biochemical analysis is in progress for these cohorts. We are also working to determine if chronic stress will effect behavioral and biochemical changes in a sex- and genotype-dependent manner in 7-month-old animals. These findings should provide important contributions to understanding stress induced sex-specific mechanism of disease.

Disclosures: H. Dong: None.

Poster

045. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 045.20/N10

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

Support: ARUK TVPG 3818

Title: Comparing knock-in and transgenic mouse and rat models of Alzheimer's disease; synaptic transmission, plaques and microglia

Authors: R. WANG¹, D. BENITEZ¹, V. C. SMITH¹, C. M. HALL¹, M. J. ROBERTS¹, N. WONG¹, C. N. E. PEERBOOM³, H. BOUTIN⁴, M. M. FERNANDES FREITAS¹, W. LIU¹, B. DE STROOPER², D. A. SALIH¹, D. M. CUMMINGS¹, *F. A. EDWARDS⁵

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Abstract: The recent introduction of knock-in mice carrying familial Alzheimer's disease mutations (Saito et al, Nat Neurosci 2014;17:661) has been a major step forward, avoiding many problems of earlier transgenic models. Here we compare two APP knock-in lines (NL-F and NL-G-F) to each other and to a transgenic line that we have previously studied. We find that much but not all of the data from the transgenic studies are validated in the knock-in mice and, by comparing the mice with different APP mutations, we can start to understand the role of insoluble versus soluble A β and its interaction with synaptic function and microglia. The earliest synaptic change detectable, both in transgenic and knock-in mice, is an increase in glutamate release probability; consistent with the proposed physiological function of A β (Abramov et al, Nat Neurosci 2009;12:1567). Interestingly, paired-pulse ratio was decreased when plaques are first detected in both the transgenic model (TASTPM, APP_{swe}/PSEN1_{M146V}; Cummings et al, Brain 2015;138:1992) and in NL-F knock-in mice, (humanised APP, Swedish and Beyreuther mutations, paired-pulse ratio 25 ms inter-pulse-interval, WT: 2.0 ± 0.11 ; NL-F: 1.2 ± 0.06 , n=13-14; P<0.0001). In contrast, in NL-G-F mice (additional Arctic mutation in the A β sequence), similar synaptic changes occur but only once the plaque load is heavy and total A β levels much higher. As most synapses are far from the small plaques initially deposited, this suggests that the early change in release depends on very low concentrations of soluble A β in the wider neuropil and that the shift in equilibrium towards insoluble A β , caused by the Arctic mutation, tends to restrict even this low level of A β more proximally to the plaques. Interactions between plaques and microglia are again similar between TASTPM and NL-F mice but also similarly delayed in the NL-G-F mice.

We also compare LTP and spontaneous synaptic activity in these different models throughout plaque development.

Finally, to assess whether an APP_{swe} transgenic rat (TgF344-AD; Cohen et al, J Neurosci 2013;33:6245), which has been reported to show advanced phosphorylation of Tau and tangle-like inclusions, would be a substantially better model, we compared the knock-in and transgenic mice to the rat. Interestingly, in both mouse and rat tissue, advanced phosphorylation of Tau is not readily seen with fluorescent immunohistochemistry or Western blot but can be clearly detected using an amplified DAB protocol. The AT8+/CP13+/PHF1+ deposits, indicating folded Tau, tend to be seen in dystrophic neurites around the plaques, which may be an early indicator of Tau pathology (He et al, Nat Med 2018;24:29) but is similar in mouse and rat.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.01/N11

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

Support: Ruth K Broad Foundation of Biomedical Research

Title: Restoration of activity in the thalamic reticular nucleus improves slow wave sleep and reduces A β deposition in Alzheimer's disease mice

Authors: *R. JAGIRDAR¹, F. M. SEIBT², J. O'MALLEY², M. BEIERLEIN², J. CHIN¹

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Abstract: Alzheimer's disease (AD) is associated with deficits in memory, attention, sleep maintenance, and slow wave sleep. The incidence of unprovoked seizures is also higher in AD patients than in reference populations. These seemingly disparate symptoms of AD all have in common the fact that they are regulated by activity in the corticothalamic network. Transgenic mice (Line J20) that express human amyloid precursor protein (APP) carrying mutations linked to AD also exhibit these symptoms. We previously described dysfunction in the corticothalamic network in these APP mice, which appears to be downstream of reduced activity in the thalamic reticular nucleus (TRN). The TRN is a critical inhibitory control nucleus in the corticothalamic network whose activity is also important for generating the slow wave activity characteristic of slow wave sleep, the phase of sleep during which metabolites such as A β are cleared from the brain. The reduction in TRN activity in APP mice was associated with sleep fragmentation and deficits in spatial memory. Therefore, the TRN may be a master regulator of many aspects of AD pathophysiology. We hypothesized that restoration of activity in TRN might be a therapeutic strategy to improve cognition and behavior, and enhance clearance of A β from the brain. Selective activation of TRN in vivo was achieved by stereotactically targeting the TRN with an AAV driving expression of CRE-dependent excitatory DREADDs. We used APP mice and nontransgenic (NTG) controls that had been crossed with mice expressing CRE in GABAergic neurons. Activation of DREADDs using CNO was confirmed in vivo by staining brain sections with a marker of activity, as well as in vitro by slice physiology. Acute activation of DREADD-expressing TRN neurons in APP mice reduced sleep fragmentation and improved slow wave sleep. Moreover chronic, daily CNO treatment (30 days) of DREADD-expressing APP mice led

to robust reductions in A β plaque load relative to saline (vehicle) treated APP mice. Together, these results demonstrate that TRN-specific expression of DREADDs enables selective activation of TRN to modify behaviour and reduce A β accumulation. Therefore the TRN may be a master regulator of pathology as well as function in several cognitive and behavioral domains in AD.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.02/N12

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

Support: NIAAG031574

Title: Ultrastructural and functional evidence of decreased white matter integrity with Alzheimer's pathology

Authors: *M. L. RUSSO, G. D. AYALA, T. F. MUSIAL, L. A. BEAN, D. A. NICHOLSON
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Abstract: Evidence suggests that the integrity of white matter (WM), consisting primarily of myelinated axons, is disrupted in response to Alzheimer's disease (AD) pathology. For instance, *in vitro* experiments have demonstrated that oligodendrocytes are sensitive to amyloid beta-induced cytotoxicity. Such findings appear to be relevant *in vivo*, as imaging studies have shown that both WM volume and fractional anisotropy decrease in early AD and mild cognitive impairment patients. These changes are particularly robust in areas highly susceptible to AD pathology, such as the hippocampus. Moreover, measures of WM integrity are significantly decreased even when controlling for changes in grey matter volume, indicating that WM changes are likely not due to Wallerian degeneration. These findings suggest that WM deterioration may represent a key pathological process in the progression of AD. Therefore, we investigated how AD pathology contributes to WM deterioration in the alveus of CA1, a major output pathway of the hippocampus. We employed electron microscopy (EM) to examine ultrastructural changes in 5xFAD mice and post-mortem human AD tissue. Measures of myelin disruption, such as myelin abnormalities and myelin thickness, were quantified using unbiased stereology. In addition, we used whole-cell current clamp to investigate if amyloid pathology alters the ability of action potentials (APs) to propagate along the axon. Specifically, a stimulating electrode placed in the alveus was used to generate APs in the axon, and successful propagation of antidromic APs was monitored using a somatic recording electrode. Our data show that myelin is substantially

disrupted at the ultrastructural level in response to AD pathology in both humans and mouse models relative to healthy controls. Electrophysiology findings indicate that this disruption corresponds to a functional deficit in the ability of CA1 pyramidal neurons to reliably propagate antidromic APs from the distal axon in the alveus back to the cell body. These results provide evidence that changes in WM tracts observed in early AD and MCI patients in imaging studies are likely indicative of changes in myelination status, and that such changes can contribute to deficits in neuronal communication.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.03/O1

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

Title: Mitigating the effects of adult obesity with exercise and dietary treatment in a mouse model of Alzheimer's disease

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Abstract: Introduction In the absence of a cure for Alzheimer's disease (AD), strategies delaying dementia onset by targeting lifestyle risk factors (>30% of attributable risk) are crucial. Here, we characterize the impact of high-fat-diet (HFD)-induced adult obesity and its rescue via changes in diet and exercise. Anatomy and memory function were examined using longitudinal structural magnetic resonance imaging (MRI), Morris Water Maze (MWM) and novel object recognition (NOR) respectively. **Methods** A transgenic mouse model of AD (3Tg) and its wild-type (WT) strain were assigned a low-fat diet (LFD) or a HFD at 8 weeks, and for the rescue, access to a wheel and/or return to LFD started at 16 weeks (n/group: 6-13). 3D T1-weighted images were acquired at 8, 16, and 24 weeks and analyzed with deformation-based morphometry. A linear mixed effect (LME) model was used to test the interaction of strain-intervention (group) combinations with timepoint (TP) using voxel-wise absolute Jacobian determinants. MWM, NOR, and brain extraction for histology were done at 24 weeks. **Results** A significant TP*group interaction (5% FDR) shows widespread increases in HFD-3Tg compared

to LFD-WT and LFD-3Tg at 16 weeks. At 24 weeks, significant decreases in volume are seen in both HFD and rescue groups, but there is a trend towards normalization in all rescues (Fig. 1). Cox fit modeling of MWM training performance suggests that HFD-3Tg are significantly worse than rescue conditions on several days of training ($p < .001$ on days 2 and 5 for the combined rescue group). **Conclusion** This study shows that obesity in the presence of mild amyloid pathology leads to accelerated aging patterns, with overall increases followed by volume loss and impaired memory. It also suggests that dietary treatment and exercise partially rescue those effects.

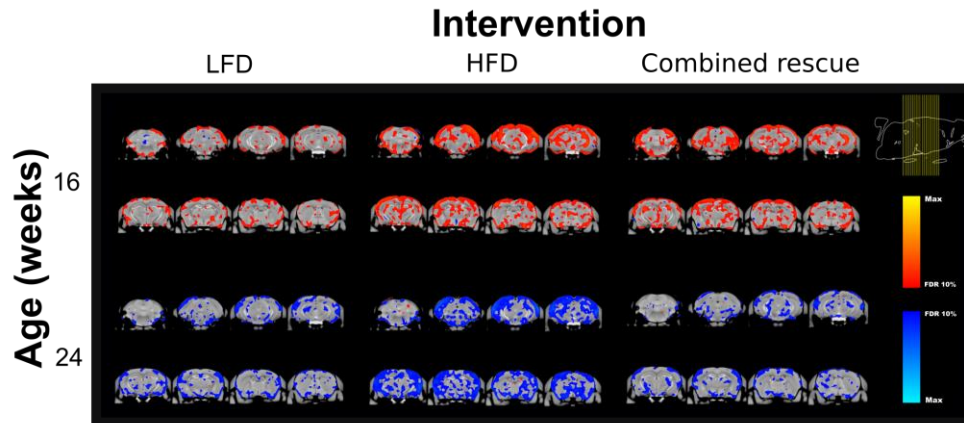


Figure 1. Visualization of LME results for 3 interventions in the 3Tg-mice overlaid on the average anatomy background. Specifically, red indicates significant (10% FDR) positive group*TP interactions while blue denotes negative interactions, with TP modelled as a quadratic term. In comparison with the LFD-WT ($n=9$), 3Tg mice maintained on the control LFD ($n=10$) undergo initial localized increases in brain volume at 16 weeks (A), followed by distributed decreases in local brain volume (D). 3Tg mice assigned a HFD from 8 weeks of age undergo significant increases in brain volume between the second and third scan (B and C). However, while 3Tg animals maintained on the HFD for 24 more weeks ($n=10$) undergo dramatic widespread decreases in local brain volume by that time (E), 3Tg mice in the combined rescue condition with exercise and return to a LFD ($n=9$) show a pattern nearly identical to that of LFD-3Tg mice, with moderate, distributed decreases in local brain volume (F). This suggests that the rescue leads to a normalization of neuroanatomical changes caused by the HFD.

Disclosures: C. Anastassiadis: None. M. Urosevic: None. C. Rollins: None. D.R. Gallino: None. V. Kong: None. G. Ayraanci: None. G.A. Devenyi: None. J. Germann: None. M. Chakravarty: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.04/O2

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

Support: QR Pharma, Inc

Lumind/RDS Foundation
Tau Consortium

Title: Reducing APP gene expression rescues endosomal defects in the Ts65Dn model of Down syndrome

Authors: *W. C. MOBLEY¹, M. MACCECCHINI², X.-Q. CHEN³

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Abstract: Down syndrome (DS), trisomy for chromosome 21, is the most common genetic cause of Alzheimer disease (AD). There is compelling evidence that increased gene dose for APP is necessary for AD in DS. Deciphering the mechanisms by which increased APP gene dose operates to cause AD in DS is important for understanding pathogenesis and discovering effective treatments. Our studies have shown that APP and its β -C-terminal fragment (β -CTF) cause dysregulation of early endosomes and that this effect is linked to atrophy of basal forebrain cholinergic neurons. Posiphen has been shown to lower APP and its fragments in a translation-dependent manner. However, whether Posiphen can reduce levels of APP and alleviate the abnormal endosomal phenotypes in DS has yet to be demonstrated. Herein, we explored the effect of Posiphen treatment on endosomal pathology in primary cortical neurons of the Ts65Dn mouse model of DS. Posiphen dose-dependently lowered the levels of full length APP and β -CTF to 2N levels and reversed the upregulation of Rab5 activity and early endosome enlargement. Concomitantly, Posiphen also normalized internalization of transferrin and the surface levels of TrkB receptors. Disrupted retrograde axonal transport and reduced BDNF signal transduction in Ts65Dn neurons were also rescued by Posiphen. These findings are further evidence linking APP gene expression to dysregulation of early endosomes in DS and suggest a role for Posiphen in treating or preventing AD in DS.

Disclosures: W.C. Mobley: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); UC San Diego. M. Maccicchini: A. Employment/Salary (full or part-time); QR Pharma, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); QR Pharma, Inc. X. Chen: 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.; UC San Diego.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.05/O3

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

Support: NASA NNX14A107G (CAL)

Title: Long-term CNS effects of proton irradiation in male and female wildtype and APP/PS1 Alzheimer's-like mice

Authors: *C. A. LEMERE¹, B. LIU¹, G. G. LIU², P. J. LORELLO³, B. CALDARONE³

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²Ann Romney Ctr. Neurol Dis, Brigham & Women's Hosp, Boston, MA; ³Genet. - Mouse Behavior Core, Harvard Med. Sch., Boston, MA

Abstract: In preparation for crewed missions into deep space, we sought to determine the long-term CNS effects of proton irradiation (IRR) on behavior and Alzheimer's disease (AD) pathogenesis in male and female C57BL/6J WT and APP/PS1dE9 Tg mice. Four mo-old Tg (18M, 18F) and littermate WT (12M, 12F) mice were exposed once to whole body IRR with 0, 50 cGy or 200 cGy protons (1000 MeV/n) at the NASA Space Radiation Laboratory at Brookhaven National Laboratory. Behavioral tests, including SHIRPA (general health), Open Field (OF), Rotarod (RR), Grip Strength (GS), Y-Maze (YM), Elevated Plus Maze (EPM), Wire Hanging (WH), Tail Suspension (TS), Acoustic Startle (AS), Pre-pulse Inhibition (PPI), Spatial Novelty Y Maze (SNYM) and Contextual Fear Conditioning (CFC), were conducted on 7-8 mice/group ~7 months post-IRR (at 11-12 mo of age). A β ELISA was used to quantify cerebral A β levels (10-16 mice/group). Hippocampal A β plaque burden and gliosis were quantified by IHC (7-8 mice/group). Proton IRR had no long-term effects on general health, basic motor and sensory function (SHIRPA), depression (TS), or sensorimotor reactivity and gating (AS or PPI). However, proton IRR had long-term effects on other outcome measures. *Locomotion* (OF, YM): Proton IRR normalized hyperactivity in female Tg mice to WT levels (50 cGy, $p < 0.05$, YM; 200 cGy, $p = 0.06$, OF) but had no effect on males. *Motor Coordination* (RR): Proton IRR significantly reduced motor coordination in male and female WT mice (50 cGy, $p < 0.05$) but had no effect on motor learning. *Strength* (GS, WH): Proton IRR modestly reduced grip strength in male WT mice (200 cGy; $p = 0.08$; GS) while both doses reduced fatigue resistance in female WT mice (50 and 200 cGy; $p < 0.05$; WH). *Anxiety* (OF, EPM): Proton IRR attenuated anxiety in male Tg (200 cGy, $p = 0.06$; EPM) and female Tg (50 cGy, $p < 0.01$; OF) mice. *Cognition* (YM, SNYM, CFC): Proton IRR significantly impaired spatial novelty memory in male Tg mice (200 cGy, $p < 0.05$; SNYM) and modestly worsened fear learning in male WT mice (50 and 200 cGy, $p = 0.06$; CFC), but improved fear learning in male Tg mice (50 cGy, $p < 0.05$), and had no effect on fear memory in any group. *A β and Gliosis*: Proton IRR had no effect on whole brain insoluble A β_{x-42} and A β_{x-40} levels, but significantly reduced hippocampal plaques and gliosis in male Tg mice (200 cGy, $p < 0.05$). Overall, proton IRR had dose-, genotype- and sex-specific effects on locomotion, motor coordination, anxiety, cognition and AD pathology. Future studies using mixed beam irradiation may help to clarify these differences to allow better assessment of the CNS risks of deep space radiation.

Disclosures: C.A. Lemere: None. B. Liu: None. G.G. Liu: None. P.J. Lorello: None. B. Caldarone: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.06/O4

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

Support: NRF 2016R1A2B4011393

Ministry of Science, ICT & Future Planning 18-BR-02-04

Title: ALWPs regulate amyloid plaque load and tau phosphorylation in a mouse model of Alzheimer's disease

Authors: ***J.-Y. LEE**¹, Y. NAM¹, Y. KOH², Y.-M. WE², H.-S. HOE¹

¹Korea Brain Res. Inst., Daegu, Korea, Republic of; ²Ctr. for Infectious Dis., Heungdeok-gu, Korea, Republic of

Abstract: Abstract

Several studies have shown that the traditional herbal medicine Liuwei Dihuang Pills (LWPs) regulates learning and memory. However, whether LWPs affect Alzheimer's disease (AD) pathology is not well studied. In the present study, we developed ALWPs, which contain LWPs and antler, and examined its effects on amyloid plaque levels as well as tau phosphorylation. We found that ALWPs administered to 5x FAD mice significantly decreased amyloid plaque levels. In addition, treatment of amyloid precursor protein (APP)-overexpressing H4 cells with ALWPs significantly reduced A β levels by altering cell surface levels of APP. Moreover, ALWPs administered to 5x FAD mice significantly decreased tau phosphorylation. Taken together, our results suggest that ALWPs may be a therapeutic drug for AD by modulating amyloid plaque load as well as tau phosphorylation.

Disclosures: **J. Lee:** A. Employment/Salary (full or part-time); Korea Brain Research Institute. **Y. Nam:** None. **Y. Koh:** None. **Y. We:** None. **H. Hoe:** None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.07/O5

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

Support: The Grant of Excellence Departments, MIUR

Title: Role of peroxisomes during adult neurogenesis in a mouse model of Alzheimer's disease

Authors: *A. FRACASSI^{1,2}, C. SCOPA^{2,3}, F. COLASUONNO², R. SCARDIGLI³, G. TAGLIALATELA¹, S. MORENO²

¹Mitchell Ctr. for Neurodegenerative Diseases, Dept. of Neurol., Univ. of Texas Med. Br., Galveston, TX; ²Dept. of Sci., Univ. Roma Tre, Rome, Italy; ³CNR-Institute of Translational Pharmacol., Rome, Italy

Abstract: Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive neuronal dysfunction/loss in the hippocampus and neocortex¹. Defective neurogenesis has been reported to exacerbate neuronal vulnerability and contribute to early memory impairment². In adult mammals, neurogenic niches include the subventricular zone (SVZ) of lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Peroxisomes are highly dynamic organelles involved in a variety of metabolic pathways, crucial for neuronal differentiation and functions. Our group described early peroxisomal changes in the brain of the Tg2576 mouse AD model (Tg)³⁻⁵, together with altered expression of their major regulators Peroxisome Proliferator-Activated Receptors (PPARs)⁶. These ligand-activated transcription factors have been suggested to be involved in neural stem cell (NSCs) fate determination^{7,8}. We investigated the role of peroxisomes in neurogenesis at the onset of AD, both *in vivo* and *in vitro*. Morphological analysis of SVZ and SGZ in Tg mice reveals stronger staining for peroxisomal membrane protein of 70 kDa (PMP70) and PPAR α , as compared to WT, as early as 1.5 mo., i.e. at pre-symptomatic stages. This is accompanied by enhanced immunoreactivity to the oxidative stress marker 8-OHG, reflecting niches altered redox homeostasis, possibly triggering early peroxisomal induction. Double immunofluorescence experiments demonstrate PMP70 expression both in Sox2⁺ NSCs and in Dcx⁺ neuroblasts, while PPAR α is only expressed in NSCs. Immunofluorescence and Western Blotting performed on neurospheres derived from 1.5-month-old Tg SVZ, confirms *in vivo* results, highlighting greater expression levels of both peroxisomal markers in Tg vs. WT. Interestingly, PMP70 appears equally expressed in Tg NSCs and neuroblasts, as well as in Tuj1⁺ neurons and GFAP⁺ astrocytes, while PPAR α preferentially colocalizes with Sox2 and GFAP, supporting the concept that PPAR α regulates glial cell fate determination of neural precursors. On the other hand, the overexpression of the two peroxisomal markers in Tg neurogenic niches suggests peroxisomal involvement at pre-symptomatic stages of the disease, related to neuronal and/or glial generation.

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Disclosures: A. Fracassi: None. C. Scopa: None. F. Colasuonno: None. R. Scardigli: None. G. Tagliatalata: None. S. Moreno: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.08/O6

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

Support: JJ Mason and HS Williams Memorial Foundation grant MAS2016F031

Title: Neither sleep disruption nor induced cortical plasticity precipitates the onset of amyloid- β pathology in an Alzheimer's disease mouse model: Preliminary data from a study of sleep and plasticity as risk factors

Authors: *M. T. KIRKCALDIE, E. A. BUCHER, A. E. KING, J. C. VICKERS
Wicking Dementia Res. and Educ. Ctr., Univ. of Tasmania, Hobart, Australia

Abstract: Alzheimer's disease is frequently modelled by transgenic mice overproducing the amyloid-beta ($A\beta$) peptide, which causes fibrillar deposits to accumulate by 4 months of age. In this exploratory study, the effects of increased production and impaired clearance of $A\beta$ on the onset of $A\beta$ deposition was examined. Weekly alternating-row mystacial whisker trimming was intended to induce cortical plasticity, while a moderate sleep disruption protocol, eight hours on an orbital shaker platform activated for 15-45 seconds at random intervals averaging two minutes for three non-consecutive nights a week, was intended to disrupt clearance (Kang et al., 2009; Sinton et al., 2009). At eight weeks of age, 12 male and 12 female APP^{swe}/PS1^{dE9} mice were assigned to four groups subjected to whisker trimming or sham, and sleep disruption or sham, in all combinations, for one month. $A\beta$ was labelled immunohistochemically using MOAB2 to show oligomeric accumulations preceding the appearance of fibrillar pathology, and epifluorescence images were segmented using the unbiased ImageSURF machine learning plugin to quantitate the amount of $A\beta$ deposits in the cerebral cortex. The total observed deposition was very small (below 0.5% in all conditions), and linear mixed effects models indicated that neither manipulation had a significant effect ($p > 0.05$ for all effects and interactions). Sex differences were not assessed, although high spontaneous death rates in female animals unrelated to experimental conditions required replacement from additional cohorts. We conclude that induced plasticity and mild sleep disruption are insufficient to hasten the onset of pathology in an overexpressing mouse model. Ongoing studies are examining the effect of several months' manipulation on animals aged six and nine months.

Kang J-E, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science*. 2009;326(5955):1005-7.

Sinton CM, Kovakkattu D, Friese RS. Validation of a novel method to interrupt sleep in the mouse. *J Neurosci Methods*. 2009;184(1):71-8.

Disclosures: E.A. Bucher: None. A.E. King: None. J.C. Vickers: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.09/O7

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

Support: BioTherapeutix LLC

Title: A neurotrophic factor mimetic improves memory retention in an aged, transgenic mouse model of Alzheimer's

Authors: *D. E. MORRISON, K. ZHANG, O. ARTAIZ, E. FERRARI, M. D. SPRITZER
Dept. of Biol. and Program in Neurosci., Middlebury Col., Middlebury, VT

Abstract: Alzheimer's disease (AD) is associated with an increased accumulation of amyloid beta (A β) peptide in the brain, which is believed to lead to cognitive impairment. Neurotrophic factors, which aid neuronal growth and survival, have shown promise for treating AD symptoms. We tested the effectiveness of a growth factor mimetic (BTX-1039) in the treatment of spatial memory deficits. The transgenic mice used in this study have three mutations that lead to overproduction of the 770 isoform of the human amyloid beta-precursor protein and associated A β in a C57BL/6J background strain. We conducted separate experiments with 8-month-old and 12-month-old mice. Mice were divided into six groups based on strain (transgenic or wild type) and drug dose (vehicle, 60 mg/kg, or 100 mg/kg). The sex ratio for each group was approximately 1:1. Mice received daily i.p. injections of 0.20 ml saline or BTX-1039 dissolved in saline for 14 consecutive days prior to starting behavioral testing. We used a Morris water maze protocol that consisted of 6 days of place-learning trials (submerged platform), 1 day of probe trials, and 3 days of cued trials (platform visible). For both age classes, the transgenic mice showed significantly longer path lengths during the place-learning trials relative to the wild type mice, indicating that the transgenes impaired spatial learning. However, there was no effect of the drug on place learning. For both age classes, the groups showed no differences in cued trials, indicating no effect of the transgenes or the drug on stimulus-response learning. For the probe trials, we observed a nearly significant impairment in memory retention among the transgenic mice relative to the wild type mice at 8 months of age and a significant impairment in the transgenic strain relative to the wild type at 12 months of age. For the 8-month-old mice, the transgenic strain injected with saline was the only group that did not perform significantly above chance levels during the probe trials. For the 12-month-old mice, transgenic groups injected with either saline or 60 mg/kg of the drug performed at chance levels during the probe trails. In summary, the results indicate that the transgenes impaired spatial memory acquisition and retention, whereas the drug improved retention specifically among the transgenic mice. This suggests that there may be some therapeutic value for BTX-1039 in the treatment of memory

impairment associated with AD. For the 12-month-old mice, brains were collected after behavioral testing, and histological staining is underway to quantify A β plaques. This will allow us to determine whether the observed effects of the drug on memory retention correlate with A β levels.

Disclosures: **D.E. Morrison:** None. **K. Zhang:** None. **O. Artaiz:** None. **E. Ferrari:** None. **M.D. Spritzer:** 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.; BioTherapeutix LLC.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.10/O8

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

Support: NIH R01 AG053060-01A1
VA 1 I01 BX002478-01A1
Florida department of Health 5AZ07

Title: Cofilin-mediated Abeta accumulation by APP endocytosis and microglial phagocytosis

Authors: ***T. LIU**^{1,2}, **J.-A. A. WOO**^{2,3}, **C. TROTTER**^{1,2}, **P. LEPOCHAT**^{1,2}, **M. Z. BUKHARI**^{1,2}, **D. E. KANG**^{1,2,4}

¹Mol. Med., ²Byrd Alzheimer's Inst., ³Mol. Pharmacol. and Physiol., Univ. of South Florida, Tampa, FL; ⁴James A. Haley Veteran's Admin. Hosp., Tampa, FL

Abstract: The accumulation of A β plays a pivotal early role in the pathogenesis of Alzheimer's disease (AD). A β levels overall are determined by the balance of production and clearance. In brain, neurons produce A β by the proteolytic processing of APP through the endocytic pathway, whereas microglia mediate a large portion of A β clearance through the phagocytic route. We previously showed that the binding of A β ₄₂ oligomers to β 1-integrin triggers Slingshot-1-mediated activation of cofilin, an F-actin-severing protein. In turn, cofilin promotes the endocytosis of cell surface β 1-integrin. As β 1-integrin and APP form surface complexes and APP endocytosis is essential for A β production, we hypothesized that cofilin might regulate cell surface APP levels and A β production. In this study, we found that siRNA knockdown of endogenous cofilin in CHO cells (7WD10) and primary neurons significantly reduces A β production by increasing surface APP levels. Expression of 'active' (S3A) but not 'inactive' (S3E) cofilin reduces surface APP levels by enhancing APP endocytosis. In agreement with results in cultured cells, A β deposition in APP/PS1 transgenic mice is significantly reduced by >50% with genetic reduction of *cofilin* (APP/PS1;*cofilin*^{+/-}). However, the reduction of A β load

in APP/PS1;*cofilin*^{+/-} mice is paradoxically associated with significantly increased microglial activation (Iba1⁺) surrounding A β deposits, suggesting a possible role for microglial clearance of A β . Indeed, 3D reconstruction of Z-stacked confocal images demonstrates significantly increased amount of A β colocalized within CD68⁺ microglia in APP/PS1;*cofilin*^{+/-} versus littermate APP/PS1 mice. Moreover, primary microglia isolated from *cofilin*^{+/-} mice demonstrate significantly higher levels of activation and phagocytic activity to both A β 42 oligomers and fibrils, indicating that genetic reduction of *cofilin* promotes A β 42 clearance via microglial phagocytosis. Taken together, our results demonstrate a surprising role of cofilin in regulating A β accumulation via both APP endocytosis and microglial phagocytosis.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/A β : Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.11/O9

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

Support: NS091969-01 NINDS

Title: Longitudinal characterization of a novel transgenic rat model of cerebral amyloid angiopathy

Authors: *D. POPESCU¹, F. XU², J. DAVIS², S. I. BEIGELMAN¹, S. SUBZWARI¹, B. J. ANDERSON¹, W. E. VAN NOSTRAND², J. K. ROBINSON²

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Abstract: Cerebral Amyloid Angiopathy (CAA) is a small vessel disease that is prevalent in the elderly and is characterized by microvascular accumulation of the amyloid β -protein (A β). It is an important driver of vascular cognitive impairment and dementia (VCID) and a prominent comorbidity of patients with Alzheimer's disease (AD). Familial CAA disorders result from mutations in the processing sequence of A β . Previously, we generated the unique Tg-SwDI transgenic mouse that produces Dutch/Iowa CAA mutant human A β in the brain and develops early-onset fibrillar cerebral microvascular A β deposition, associated neuroinflammation, and behavioral deficits. However, relative to rats, mice are limited in terms of exploring specific cognitive deficits. Therefore, we have generated a new rat model, rTg-DI, with the same familial Dutch/Iowa CAA mutations. Initial analyses of histopathology of the rTg-DI show a progressive and robust accumulation of small vessel fibrillar amyloid starting at three months of age. We also performed extensive behavioral analyses including operant discrimination, working memory,

attention and motor production paradigms. Initial analyses of these data suggest the prime impairments may be perceptual and sensory-motor in nature, both of which are characteristics of CAA in humans. Keywords: Cerebral Amyloid Angiopathy, Alzheimer's Disease, rodent model

Disclosures: D. Popescu: None. F. Xu: None. J. Davis: None. S.I. Beigelman: None. S. Subzwari: None. B.J. Anderson: None. W.E. Van Nostrand: None. J.K. Robinson: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.12/O10

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

Support: CIHR
Brain Canada

Title: Strategies for quantifying behavioral changes in primate models

Authors: *R. G. WITHER¹, S. E. BOEHNKE¹, R. A. MARINO¹, J. Y. KAN¹, A. LABLANS¹, B. HYDUK¹, R. LEVY¹, F. G. DE FELICE², D. P. MUNOZ¹

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Abstract: Development of non-human primate models of neurological disease has rapidly increased in the past decade. In order to test the efficacy of therapeutics *in vivo*, a primate model must have trackable biomarkers. Behavioral and cognitive changes serve as a compelling proxy for neurological changes, and ideally these would be correlated with changes in other biomarkers (neuroimaging, CSF, blood, and brain pathology). Our group has been developing primate models of neurodegenerative disease and has recently developed a macaque monkey model of AD via intracerebroventricular (icv) injection of neurotoxic amyloid beta oligomers (A β O). This model recapitulates the molecular aspects of human AD pathology, such as tau hyperphosphorylation coupled with tangle formation, synaptic loss, and astrocytic activation (Forny-Germano et al., J.Neurosci, 2014, Batista et al., J. Path, 2018). In developing a behavioral platform to examine the effects of these injections, we aimed to maximize the translational value of the study by examining learning and memory performance through tasks that have been validated in human AD patients. Using a cage-side touch-screen adapted version of the human CANTAB AD battery (Monkey CANTAB, Lafayette), we tested the cognitive profile of our A β O injected macaques using tasks that assessed focused attention, spatial working memory, visual discrimination, and paired associates learning capacities. To further enhance the translational potential of the study, we examined both the ability of injected macaques to retain previously learned tasks, as well as their ability to learn new tasks. We also monitored home-

cage behavior by examining the circadian rhythms and behavioral patterning of the macaques using a 3-D accelerometer activity tracker (Actical) and 24/7 video monitoring with a custom home-cage behavior video coding program developed in Matlab. Using this behavioral platform, we were able to observe focused attention and spatial working memory deficits on the self-ordered spatial search task in macaques following A β O injection, as well as changes in the strategies utilized to solve the task. Furthermore, we observed that injected macaques had difficulty learning new tasks (delayed match to sample and paired associated learning). In addition to learning and memory deficits, overall home-cage activity and behavioral patterning was individually altered post injection. Overall, here we present a viable behavioral platform by which to evaluate the development of AD in primates, which can be easily translated to track disease progression in other primate models.

Disclosures: R.G. Wither: None. S.E. Boehnke: None. R.A. Marino: None. J.Y. Kan: None. A. Lablans: None. B. Hyduk: None. R. Levy: None. F.G. De Felice: None. D.P. Munoz: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.13/O11

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

Support: CONICYT-AFP 170005 to NCI
EU-LAC T010131 to NCI
FONDECYT 11160651 to PC

Title: Octodon degus, toward its consolidation as a natural model of Alzheimer`s disease

Authors: *J. M. ZOLEZZI¹, P. CISTERNAS², N. C. INESTROSA³

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Abstract: Alzheimer`s disease (AD) is the leading cause of age-related dementia worldwide. No therapy is currently available to stops or reverses the progression of AD. Because of the disappointing results obtained in different clinical trials, the identification of new therapeutic alternatives and more reliable models of AD are very important. In this regard, *Octodon degus*, a Chilean rodent has been found to spontaneously develop neuropathological signs of AD, including amyloid- β peptide (A β) aggregates, as well as post-synaptic dysfunction. Aging is an important factor in the cognitive function impairment exhibited by *O. degus*, which can be related with a decrease in synaptic function and the appearance of AD pathological hallmarks.

Moreover, the capacity of *O. degus* A β to aggregate constitutes a relevant issue toward its usefulness as a natural AD model. Thus, in the present work, we study the capacity of *O. degus* A β ₁₋₄₀ to aggregate *in vitro* and to form oligomers and amyloid fibrils, evaluated at the electron microscopy level. Moreover, we evaluated the appearance and distribution of thioflavin-S, 6E10 and 4G8 positive amyloid plaques during aging in “wild-caught *O. degus*”, and compared them with the amyloid plaques present in two different transgenic mice, the double transgenic APP/PS1 and the J20 transgenic AD mouse models, including with an evaluation of its three-dimensional structure. Amyloid plaques first appear in anterior brain structures of *O. degus* around 32 month-old, and in the whole brain after 56 month-old. Although the total number of plaques (N° plaques/mm²) was lower than in transgenic animals, the amyloid plaques size was bigger in old *O. degus* brains in comparison with the transgenic mice used for comparison. Consistent with our previous works, our current findings allows us to conclude that under specific environmental conditions *O. degus* develops several molecular and physiological alterations resembling the AD pathophysiology, including the age-related progression of A β aggregates across the brain. Therefore, we confirm that the Chilean rodent *Octodon degus* constitutes a “natural” model of AD, and constitutes a valuable tool to search for therapeutic strategies against AD.

Disclosures: J.M. Zolezzi: None. P. Cisternas: None. N.C. Inestrosa: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.14/O12

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

Support: Commonwealth of Virginia’s ARDRAF Award No. 18-1

Title: Vascular amyloidosis, astrocytic endfeet, and blood-brain barrier disruption

Authors: *W. A. MILLS, III¹, I. F. KIMBROUGH², L. CHAUNSAI³, A. STUBLEN², H. SONTHEIMER^{2,3}

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Abstract: The blood-brain barrier (BBB) is a specialized brain endothelial structure that tightly regulates the bidirectional passage of components between the brain and blood. This is accomplished by the presence of tight junction and adherent junction proteins, along with numerous transport systems. Although initially induced by pericytes, tight junction proteins are both stabilized and maintained by astrocytes due to close physical contact of the astrocytic membrane with the blood vessel. In a previous study, we demonstrated that disruption of

astrocytic contact due to invading glioma cells resulted in loss of the tight junction proteins zonula occludens-1 (ZO-1) and claudin-5, along with focal breaches of the BBB¹. We also recently showed in the hAPPJ20 mouse model of familial Alzheimer Disease that vascular amyloid accumulates between the vessel and astrocytic endfoot, ultimately leading to endfoot separation². To assess whether a loss of endfeet by accumulating vascular amyloid causes BBB impairments we employed Cadaverine, a 1kDa fluorescent blood tracer that is taken up by neurons upon leakage into the brain. We find an increased number of Cadaverine positive cells compared to age-matched controls in the cortex only in regions with vascular amyloid laden vessels. This finding was corroborated through *in vivo* multiphoton imaging through a cranial window revealing leakage of fluorescent dextran only at vessels with vascular amyloid deposits. Further immunohistochemical analysis of tissue from hAPPJ20 mice shows loss of the tight junction proteins ZO-1 and Claudin-5, as well as the glucose transporter GLUT1 on amyloid containing blood vessels. While this loss correlated with vascular amyloid accumulation and endfoot separation, the causal relationship between amyloid and loss of tight junction proteins remains to be determined. It is possible that loss of tight junction proteins is secondary to impaired angiopoietin- src-suppressed C kinase substrate signaling, through which astrocytes are believed to promote tight junction expression. Alternatively, amyloid may exert toxicity directly to endothelial cells with endfoot retraction being a secondary event. Ongoing imaging studies using targeted two-photon chemical apoptotic ablation (2Phatal) will determine if astrocytic endfoot contact is necessary to maintain BBB integrity.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.15/O13

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

Support: NSERC Discovery Grant #40352
NSERC #RGPIN-2017- 03857
Alberta Neuroscience Program Grant

Title: Probing cortico-cortical and hippocampal-cortical interactions in a second-generation mouse model of Alzheimer's disease

Authors: *S. SINGH¹, J. MEHLA², R. J. SUTHERLAND², M. H. MOHAJERANI²
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Abstract: It is known that Alzheimer's disease (AD) is associated with defects of synaptic connectivity. Such defects may not be restricted to local neuronal interactions but may extend to long-range brain activities, such as slow-wave oscillations that are particularly prominent during non-rapid eye movement (non-REM) sleep and are important for integration of information across distant brain regions involved in memory consolidation. Using a newly characterized knock-in mouse model of AD (n = 8, 12 months old) that has humanized amyloid beta (A β) sequence knocked-in to the murine amyloid precursor protein gene along with the Swedish, Arctic, and Beyreuther/Iberian mutations (APP NL-G-F), and wide-field optical imaging of cortical voltage responses (VSDI) combined with local field potential (LFP) recording from CA1, we investigated that how A β deposition in these mouse model impacts cortical functional connectivity and how different cortical regions interact with hippocampus during slow wave sleep. We found that A β deposition in knock-in mouse model of AD (APP NL-G-F) impairs cortical functional connectivity and intrinsic hippocampal circuit that generates SWR. Coordination of cortical up-states and hippocampal sharp-wave ripples (HPC-SWR) during slow wave sleep is believed to play a major role in the consolidation of recently acquired memories. It was observed that HPC-SWR show strong correlation with cortical activation in retrosplenial cortex (RSC). However, the magnitude of ripple power and cortical activation in RSC is reduced in AD mice as compared littermate controls, suggesting impairment in hippocampal-cortical interaction during slow wave sleep. We further analysed cortical VSDI data from 19 region of interests (ROIs) with two nonlinear methods: entropy (En) and auto mutual information (AMI). En quantifies regularity in data, while AMI detects linear and nonlinear dependencies in time series. We observed that En was lower in AD mice, and AMI decreased more slowly with time delays in AD as compared to control mice, for both En and AMI significant differences were observed in occipital, somatosensory and motor cortex (p<0.05). These results provide new insights into brain dysfunction associated with A β deposition in APP NL-G-F mouse model of AD.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.16/O14

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

Title: APP-directed antisense oligonucleotides reduced APP gene expression in mouse models of Down Syndrome

Authors: *M. SAWA¹, H. ZHAO², H. KORDASIEWICZ², B. FITZSIMMONS², D. DERSE¹, A. BECKER¹, C. OVERK¹, W. C. MOBLEY¹

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Abstract: Early onset of Alzheimer disease (AD) is observed in most adults with Down syndrome (DS); the condition is referred to as AD in DS. The pathology of AD is routinely present by age 40 years and more than 50% of those with DS are demented after age 55. Clinical observations point to a necessary role for a third copy of the APP gene for AD in DS. Studies in the Ts65Dn mouse model of DS are in accord with human observations, demonstrating a necessary role of increased APP gene dose for degeneration of locus coeruleus neurons and cholinergic neurons of the basal forebrain. A rational therapeutic objective to prevent AD in DS is to reduce APP gene expression prior to onset of AD pathogenesis. In one approach we turned to antisense nucleotides (ASOs) directed against APP RNA. Following in vitro screening of candidate mouse ASOs, the most effective ASO (mAPP-ASO1) was further evaluated in vitro and in vivo using the Ts65Dn and Dp16 models of DS, each of which harbors an extra copy of mouse APP in a mouse chromosomal region homologous to human Ch21. In vitro assays using cortical neurons confirmed dose-responsive reductions in APP mRNA and protein to levels present in 2N cells. In in vivo assays, 8 weeks following a single intracerebral ventricular injection of mAPP-ASO1 (500 ug) in Ts65Dn mice, APP gene expression was reduced to 2N levels with respect to APP mRNA, the APP full length protein and Abeta 42 and 40. In another measure of efficacy, the increase in early endosome size, a marker of AD pathogenesis in DS that is caused by increased APP gene expression, was also normalized by mAPP-ASO1. Our data are evidence that mAPP-ASO engaged APP RNA to normalize APP gene expression and reverse a marker of AD pathogenesis. The results suggest that by reducing APP gene expression APP-directed ASOs may act to intercept the AD pathogenesis in DS.

Disclosures: **M. Sawa:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Ionis Pharmaceuticals. **H. Zhao:** A. Employment/Salary (full or part-time);; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock holder of Ionis Pharmaceuticals. **H. Kordasiewicz:** A. Employment/Salary (full or part-time);; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock holder of Ionis Pharmaceuticals. **B. Fitzsimmons:** A. Employment/Salary (full or part-time);; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock holder of Ionis Pharmaceuticals. **D. Derser:** None. **A. Becker:** None. **C. Overk:** None. **W.C. Mobley:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Ionis Pharmaceuticals.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.17/O15

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

Support: R01 AG037919

RF1 AG056371

R56 AG057565

K01 AG044490

AARF-16-443213

Title: Effect of TREM2 deficiency on the phenotype of APP/PS1 mice expressing human APOE isoforms

Authors: *C. WOLFE, N. FITZ, B. PLAYSO, K. NAM, F. LETRONNE, I. LEFTEROV, R. KOLDAMOVA

Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Alzheimer's disease (AD) is the leading cause of dementia worldwide and is characterized by amyloid β accumulation, tau pathology, and associated increased neuroinflammation. The strongest known genetic risk factor for late-onset Alzheimer's disease (LOAD) is the inheritance of ApolipoproteinE4 (APOE4). Multiple animal models and human data have defined APOE isoform-specific differences in amyloid β clearance and development of amyloid plaques. Specific disease variants in the triggering receptor expressed on myeloid cells 2 (TREM2) gene have been identified by GWAS as a potential risk factor for AD. TREM2 encodes a receptor exclusively found on immune cells, such as microglia, indicating a role in immune response for in the pathogenesis of AD. Binding of TREM2 and APOE potentially occurs in an isoform dependent manner, which could influence microglia-mediated phagocytosis; however the biological significance, and the interconnected role of TREM2 with APOE in AD pathology, is not well understood. We hypothesize that in mice with an AD-like phenotype, TREM2 deficiency in both human APOE3 and APOE4 targeted replacement mice will exhibit worse performance in memory specific behavioral tests, and reduce the microglial barrier around plaques, leading to more diffuse plaques and protofibrillar A β buildup around plaques. To test the hypothesis we have performed novel object recognition, and contextual-cued fear conditioning behavioral testing on male and female, 6-month-old mice expressing human APOE3, or APOE4, APOE3/Trem2^{+/-}, APOE3/Trem2^{-/-}, APOE4/Trem2^{+/-}, and APOE4/Trem2^{-/-} on both WT and APP/PS1 Δ E9 genetic backgrounds. Following the behavior testing, brain tissue was collected for histological analysis of amyloid deposition (6E10, Thioflavin S, OC), microglia reactivity (IBA1), and neuronal dystrophy. We measured the spatial relationship

between the microglial barrier surrounding senile plaques, soluble forms of amyloid β and correlated this relationship to neuronal dystrophy. Considering the current understanding of the relationship between the function of TREM2 and APOE isoform, the results of this study establish behavioral and histological differences in amyloid deposition associated with TREM2 deficiency in mice expressing human APOE3 or APOE4 isoform.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.18/O16

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

Support: Protein Folding Diseases Initiative - University of Michigan

Title: A novel conditional mouse model of amyloidogenesis

Authors: *L. J. OUILLETTE¹, R. PARENT², H. BURNS¹, A. SMARSH¹, V. A. CAZARES³, S. J. MOORE⁴, G. G. MURPHY⁵

²Mol. and Behavioral Neurosciences Inst., ³Mol. and Behavioral Neurosci. Inst., ⁴Mol. & Behavioral Neurosci Inst., ⁵MBNI/Physiology, ¹Univ. of Michigan, Ann Arbor, MI

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder that represents the most common form of dementia. It is characterized by intracellular neurofibrillary tangles (NFTs), which are composed primarily of aggregates of hyper-phosphorylated microtubule-associated tau protein, and also amyloid plaques which are aggregated extra-cellular amyloid beta (A β) protein. The role of A β in AD has been further substantiated by the identification of genetic mutations in the A β precursor protein (APP) itself and in presenilin 1 & 2 (PS1 & PS2), enzymes known to be involved in the processing of APP to A β . Mutations in these genes have been associated with neurodegeneration as a component of the late stage pathology seen in AD.

We have generated a new line of transgenic mice that overexpress both mutant human APP as well as human PS1 that allows the flexibility to obtain cell type specificity and temporal control of expression of mutated proteins. The mutations inserted into human APP(695) were the Swedish (K670N, M671L), Florida (I716V), and London (V717I) and the mutations associated with PS1 were M146L and L286V. We have inserted an excisable stop codon between a CAG promoter and the transgenes that consists of a LoxP-stop-LoxP sequence, which allows the pattern of expression to be dependent on the distribution of cre-recombinase. Mice were generated by pronuclear injection of both constructs. Our preliminary data suggests that both the mutated APP and PS1 transgenes integrated into the same location, as both transgenes transmit

to 100% of the offspring as confirmed by polymerase chain reaction using primers specific to either transgene. Founders containing the transgenes were crossed with transgenic mice in which the expression of cre-recombinase is regulated by the SynapsinI promoter which provides pan neuronal expression. Additional characterization is ongoing.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.19/P1

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

Support: RO1AG058171

Title: Changes in dorsal hippocampal calcium levels and behavior before, during, and after AD pathology in the 5XFAD mouse

Authors: *A. O. GHOWERI¹, L. OUILLETTE², H. N. FRAZIER¹, K. L. ANDERSON¹, J. C. GANT¹, R. PARENT², G. G. MURPHY², O. THIBAUT¹

¹Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY; ²Physiol., Univ. of Michigan, Ann Arbor, MI

Abstract: As the projected rise of individuals affected by Alzheimer's disease is expected to triple by 2050, the need for the characterization of associated molecular mechanisms and the development of novel therapeutic treatments is indispensable. One potential mechanism highlighted in the calcium hypothesis of brain aging and dementia, describes a state of altered calcium handling in neurons that has an impact on several physiological parameters, including an increase in the Ca-dependent potassium potential, the afterhyperpolarization (AHP). One hallmark marker of neuronal aging in field CA1 of the hippocampus is the increase in the AHP, accompanied with elevated levels of calcium (Landfield & Pitler, 1984; Thibault & Landfield, 1996; Thibault et al., 1994). Though the strong association between calcium and the AHP has been illustrated in normal aging, how the two phenomena contribute to disease-state aging remains largely unknown and perhaps even less is known in models of AD. Recent work has reported reduced levels of L-type voltage sensitive calcium channels (L-VSCCs) in older APP and PS-1 transgenic mice, suggesting calcium dysregulation in AD mouse models may vary from that seen in aging (Thibault et al., 2012; Berkowitz et al., 2017). In this study, we are identifying the effects of aging on the calcium-dependent afterhyperpolarization and intracellular calcium levels in the 5XFAD model on a C57Bl6 congenic background. Using sharp electrode electrophysiology and calcium imaging (OGB-1), we are seeing an attenuated AHP in the

transgenic animals compared to the wildtype animals at 4 months of age. Analyses of behavior data (MWM) does not show deficit until later (6-7 months). This evidence suggests that reduced neuronal calcium signaling, as opposed to elevated calcium signaling could be a precipitating factor in the manifestation of behavioral deficits.

Overall these data corroborate the decreased L-VSCCs see in previous studies from our group and suggest alteration in behavior is not always tied to an increase in neuronal calcium. Indeed, calcium levels and kinetic analyses are suggesting reductions in calcium handling could well increase excitability and stimulate the onset of cognitive decline. Such measures provide new insights into dysregulated calcium and neuronal health, and directly address disease phenotype progression over time.

Disclosures: **A.O. Ghoweri:** None. **L. Ouillette:** None. **H.N. Frazier:** None. **K.L. Anderson:** None. **J.C. Gant:** None. **R. Parent:** None. **G.G. Murphy:** None. **O. Thibault:** None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

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Program #/Poster #: 046.20/P2

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

Support: NIH Grant 5R01AG030142-08
BrightFocus Foundation

Title: Absence of tau does not prevent dystrophic neurite formation in two Alzheimer's disease mouse models

Authors: ***S. KEMAL**, R. J. VASSAR
Cell and Mol. Biol., Northwestern Univ., Chicago, IL

Abstract: Brain pathology of Alzheimer's disease (AD) patients shows intra-neuronal neurofibrillary tau tangles and extracellular beta amyloid (A β) plaques. Plaque regions are surrounded by swollen dystrophic neurites filled with vesicles. Mouse models of AD rely on the introduction of familial mutations that recapitulate some of the pathology observed in human AD patients. The 5XFAD line overexpresses mutant amyloid precursor protein (APP) and presenilin-1 (PS1), resulting in rapid (within ~2 months) amyloid deposition, neuroinflammation, and dystrophic neurite formation. More recently, another AD model, the APP^{NL-G-F} mouse, employs a knock-in approach to express mutant APP at endogenous levels, thereby circumventing any potential artifacts of overexpression. The APP^{NL-G-F} line also exhibits early plaque development accompanied by neuroinflammation. Less is known about dystrophic neurite formation in these mice.

We separately crossed the 5XFAD and the APP^{NL-G-F} models with a tau-knockout line to assess

the effect of tau removal on brain pathology in these two AD models. Tau is a microtubule associated protein that has a role in microtubule stability. Hyper-phosphorylation of tau causes it to disengage from the microtubule and form aggregates. In vitro and behavioral studies have previously indicated that the presence of tau is required for A β -induced toxicity and memory deficits. Using immunohistochemical and biochemical means, we examined the formation of dystrophic neurites, A β plaques, and the extent of neuroinflammation in the tau-deficient AD mouse brains at various ages and found that they are not significantly altered compared to tau wild-type AD mouse brains. These results suggest that much of the pathology observed in AD is tau-independent.

Growing evidence points to amyloid plaque burden as being central to subsequent treatment outcomes for AD patients. Given the recent failures with clinical trials, it is important to assess the independent contributions of A β and tau to the progression of AD. Studies such as this are crucial to elucidating the mechanism by which A β and tau cause AD pathology, and ultimately inform treatment strategies.

Disclosures: S. Kemal: None. R.J. Vassar: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.21/P3

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

Title: Effects of chronic stress on anxiety- and fear-like behaviors in the TgF344-AD rat model of Alzheimer's disease

Authors: *S. BOUQUIN¹, C. R. MAESTAS-OLGUIN², A. A. TOURIGNY², B. J. CLARK³, N. S. PENTKOWSKI²

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Abstract: Alzheimer's disease (AD) is a significant health problem that has no treatments. The inability to treat AD is attributed in part to an incomplete understanding of the neurobiology underlying its pathophysiology. A common risk-factor for AD may involve exposure to chronic stress. AD research has recently focused on the corticotropin-releasing factor (CRF) signaling system in mediating the development of AD related pathophysiology. For example, CRF type-1 (CRF₁) receptor-dependent accumulation of amyloid-beta (AB) and aggregation of hyperphosphorylated tau proteins have been reported in mouse models. However, these models are limited as they do not manifest the full AD-related pathophysiology (e.g., AB plaques, neurofibrillary tangles (NFTs), neuroinflammation and cell loss) that normally progresses. The recently developed Tg+ rat model of AD (TgF344-AD) expressing the mutant human amyloid precursor protein (APP^{sw}) and presenilin 1 (PS1 Δ E9) genes are susceptible to progressive

accumulation of AB plaques, NFTs, neuroinflammation and cell loss. We recently reported that Tg+ rats exhibit enhanced anxiety-like behavior at time points (6 months) prior to the development of AD-related neuropathology, a finding that has also been shown to precede the expression of cognitive difficulties in AD patients. However, it is unclear whether these behavioral deficits involve CRF signaling, or whether chronic stress can potentiate AD-related pathology including heightened anxiety and cognitive decline. This study sought to examine the effects of chronic restraint stress on CRF₁ expression in key regions altered in AD (e.g., hippocampus & prefrontal cortex), and to determine the influence of chronic stress on anxiety- and fear-like behaviors. At 6 months of age, Tg+ and WT rats were stressed daily for 1-hour across 14 consecutive days; controls were briefly handled daily. Next, rats were tested for anxiety-like behaviors in the elevated-plus maze and light-dark test, and for fear-like behavior following footshock contextual conditioning. Following testing, rats were perfused and 40 µm coronal sections were collected across the entire rostral-caudal extent of the hippocampus and prefrontal cortex. Subsequently sections were processed for CRF₁ immunoreactivity using nickel-enhanced DAB, and CRF₁ positive cells were quantified using ImageJ. Like our previous report, Tg+ rats exhibited increased anxiety-like behaviors but did not show differences in conditioned fear compared to WT controls. Surprisingly, our initial analysis failed to detect reliable stress effects between Tg+ and WT rats. Comparison of CRF₁ expression between is currently being analyzed.

Disclosures: S. Bouquin: None. C.R. Maestas-Olguin: None. A.A. Tourigny: None. B.J. Clark: None. N.S. Pentkowski: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.22/P4

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

Title: Effects of tart cherry extract on neuroinflammation and cognitive function in 5xFAD animal models of Alzheimer's disease

Authors: *Z. BOWERS¹, P. MAITI³, D. SENGUPTA⁴, G. L. DUNBAR²

¹Neurosci., Central Michigan Univ., Freeland, MI; ²Neurosci., Central Michigan Univ., Central Michigan University, MI; ³Psychology and Neurosci. Program, ⁴Central Michigan University/St. Mary's of Michigan, Saginaw, MI

Abstract: Neuroinflammation and deposition of misfolded amyloid proteins are the hallmark pathologies observed in Alzheimer's disease. These pathological changes are involved in progressive neurodegenerative changes, including neuronal loss and synaptic failure in selective brain regions, which are associated with cognitive deficits in AD. Current treatments regimen show unsatisfactory outcomes with limited availability, which requires new therapeutic

development. Recently, several natural anti-oxidant, anti-amyloid polyphenols have been tested by many researchers in different animal models of AD. In the present study, we aimed to investigate and compare the effects of the polyphenols derived from tart cherry extract (TCE) in animal models of AD. The 6 and 12 months old 5xFAD mice (n=8/group) will be administered with TCE (60 mg/kg), by oral gavage with every other day for 2 months period, while age-matched control mice will receive the similar amount of vehicle (0.5% methyl cellulose in PBS). After stipulated period of experiment, a battery of behavioral tests, such as open field test, novel object recognition task and Morris water maze will be performed to test the animal cognitive functions. Following behavioral paradigm, the brains will be collected for investigation of neuroinflammatory markers and amyloid proteins levels. It is anticipated that the mice which receive TCE will show less neuroinflammation, decrease amyloid plaques and may improve neurobehavioral deficits compared to age matched wild-type mice. It is also expected that treatment with 6 month old 5xFAD mice will show greater neuroprotective outcomes compared to 12 months old mice. Overall, this comparative study will give an insight overview of neuroprotective mechanism of TCE in animal models of AD.

Disclosures: **Z. Bowers:** None. **P. Maiti:** None. **D. Sengupta:** None. **G.L. Dunbar:** None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

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Program #/Poster #: 046.23/P5

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

Support: NIH Grant F31AG046087
NIH Grant R01 NS096275 01

Title: The non-transcriptional role of hif-1a in the activation of g-secretase in the brain

Authors: ***T. LI**^{1,3}, **C. CARROLL**³, **D. CHIU**³, **A. BRANDES**³, **Y. HATTORI**², **C. IADECOLA**¹, **Y. LI**⁴

²Feil Family Brain and Mind Res. Inst., ¹Weill Cornell Med., New York, NY; ³Mem. Sloan Kettering Cancer Ctr., New York, NY; ⁴Mem. Sloan-Kettering Cancer Ctr., New York, NY

Abstract: Alzheimer's disease (AD) is the sixth leading cause of death in the US, and there is currently no effective treatment or cure. One major risk factor for developing AD is hypoxia i.e., as a result of a stroke. Understanding the relationship between hypoxia and AD may provide insight to future therapeutics. g-Secretase is an intramembrane aspartyl protease composed of four obligatory subunits (presenilin (PS), nicastrin (NCT), Aph1, Pen-2) for protease activity that cleaves multiple type I membrane proteins. The most prominently known and studied substrates are amyloid precursor protein (APP) and Notch receptor proteins. APP is first cleaved by either

α - or β - secretase, followed by cleavage by g-secretase. If APP is first processed by b-secretase, subsequent cleavage by g-secretase produces amyloid beta (Ab) peptides of varying lengths. These peptides can then oligomerize and form the hallmark amyloid plaques found in AD brains. Previous reports have shown that hypoxia increases Ab production in both cells and mice. In this study, we aim to show that this increase in Ab is due to an increase in g-secretase activity. Additionally, we assess the role of Hif-1a, the master regulator of hypoxia, on g-secretase activity and we demonstrate that g-secretase activity and production of Ab is independent of its canonical, transcriptional role.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

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Program #/Poster #: 046.24/P6

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

Support: R01ES026057
R01ES026067-S2

Title: Early and persistent sex-differences in the age-associated increase of amyloid beta in 3xtg-ad mice

Authors: *J. R. RICHARDSON, A. EID, M. EDLER, I. MHATRE, C. CRISH
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Abstract: Alzheimer's disease (AD) is characterized by amyloid-beta (A β) plaques and neurofibrillary tangles (NFTs). Plaques are comprised of extracellular aggregates of A β 40 and A β 42 peptide fragments, sequentially cleaved by secretases from the amyloid precursor protein (APP). NFTs are formed by the aberrant phosphorylation and folding of the microtubule associated protein tau (MAPT). Aging, family history, female sex and the APOE ϵ 4 genotype have been shown to play prominent roles in AD risk, but little is known about interaction of aging and sex in amyloid deposition. Previous work by Carroll and colleagues (2010) demonstrated that A β load, measured by immunohistochemistry, was increased in the cortex of females compared to males as early as 6 months of age in 3xTG-AD mice that carry familial AD mutations of PSEN1 (M146B), APP (KM670/671NL), and MAPT (P301L). In this study, we used a multiplex protein system to quantify the levels of A β 38, 40 and 42 from 1-17 months of age in male and female 3xTg-AD mice across all time points in the hippocampus and frontal cortex. As early as 1 month of age, A β 40 and 42 levels were 2-3 fold higher in female 3xTG mice compared to male 3xTG in both the frontal cortex and hippocampus. At 12 months of age,

female mice had 3-fold higher levels of A β 40 levels in the hippocampus and cortex, 5- and 10-fold higher A β 42 in the frontal cortex and hippocampus compared to age-matched male mice. Similar findings were observed for A β 38 in both regions, with females exhibiting approximately 2-fold higher levels as compared to age-matched males. These data demonstrate that A β levels can be reliably detected in brain as early as 1 month of age and that female 3xTG mice generate A β at much higher levels than the males. Future studies will examine potential mechanisms responsible for increased A β production in female 3xTG mice.

Disclosures: J.R. Richardson: None. A. Eid: None. M. Edler: None. I. Mhatre: None. C. Crish: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.25/P7

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

Support: NIGMS 5P20GM109025

Title: GABA-specific changes in a mouse model of Alzheimer's disease

Authors: *A. M. LEISGANG, A. M. SALAZAR, A. ORTIZ, J. W. KINNEY
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Abstract: Alzheimer's Disease (AD) is neurodegenerative disease clinically described as the progression of learning and memory deficiencies. Pathologically, AD is characterized by the presence of three core features: beta-amyloid plaques (A β), neurofibrillary tangles (NFT), and chronic neuroinflammation. Several mechanisms are proposed to be responsible for impaired learning and memory, neuroinflammation, and progressive neuronal loss including alterations in several transmitter systems. Gamma amino butyric acid (GABA), the principal inhibitory neurotransmitter in the brain, are demonstrated to be essential in learning and memory. As these deficiencies are reported in clinical populations and animal models of AD, a more careful examination of GABAergic changes in AD progression is needed.

Our previous study in a 6-month-old APP/PS1 mice demonstrated that there are significant changes in several GABAergic signaling mechanisms, in comparison to wildtype. This led us to the current study in which we analyzed the alterations in the GABAergic signaling in four cohorts of APP/PS1 mice at different ages (9, 7.5, 6, and 3-4 months), to identify the timepoint when the changes emerge and persist through later timepoints. The mice were subjected to learning and memory tasks to identify deficiencies compared to wildtype. The total protein and mRNA levels for GABAergic targets were measured. Our data indicate that changes in the GABAergic signaling happens around 4 months of age and persist through their life span.

Interestingly, our data also indicate that the emergence of alterations in GABAergic signaling coincide with the same timepoints at which learning and memory deficits and A β pathology arise in the APP/PS1 mouse model. These further demonstrate that changes in GABA may underline pathological changes observed in AD. Our study supports the need for further investigation of specific GABAergic changes in the progression of AD.

Disclosures: A.M. Leisgang: None. A.M. Salazar: None. A. Ortiz: None. J.W. Kinney: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.26/P8

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

Support: Fondo Mixto del Estado de Jalisco FOMIXJAL 2014-01-250508
Coriell Institute for Medical Research

Title: Alzheimer's disease modeling using induced pluripotent stem cells carrying an A246E mutation in PSEN1

Authors: *M. A. HERNANDEZ-SAPIENS¹, E. E. REZA-ZALDIVAR², R. R. CEVALLOS⁴, Y. K. G. GUTIERREZ-MERCADO, 44270², A. L. MARQUEZ-AGUIRRE^{2,3}, K. GAZARIAN⁵, A. A. CANALES-AGUIRRE²

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Abstract: Alzheimer Disease (AD) is characterized by the progressive aggregation of β -amyloid (A β) around neurons and the intracellular accumulation of neurofibrillary tangles of hyperphosphorylated tau, mainly in areas implicated in memory and learning as prefrontal cortex and hippocampus. There are two forms of AD, late-onset AD (or sporadic) that affects people over 60 years old, and the early-onset AD (or familial) which is hereditary and represents almost 5% of all cases. Unfortunately, there is no cure for AD, for that reason, it is important to identify molecular targets implicated in disease spread throughout the brain. Currently, the generation of induced pluripotent stem cells (iPSCs) through the cell reprogramming of adult somatic cells, allows the development of new cellular models of different pathologies, such as AD, which can be used to study the molecular pathogenesis in a personalized way and evaluate therapeutic candidates. Therefore, the aim of this study was to implement an AD tridimensional cell culture model using iPSCs carrying the A242E mutation. Here we generated and established two human iPSC cell lines, one from patient's fibroblasts with AD inherited carrying A246E mutation in the PSEN1 gene (Kindly donated by Coriell Institute for medical research) and other from fibroblasts without mutation, were performed using lentiviral vectors with the

OSKM factors (Oct4, Sox2, Klf4, c-Myc). The resulting iPSC cell lines expressed pluripotency genes (like Nanog and Oct4), active alkaline phosphatase activity and common pluripotency markers expression (such as SSEA4, Tra-1-60). Neural differentiation was carried out through dual SMAD and TGF-B signaling inhibition. These iPSC cell lines exhibit the ability to differentiate into neuronal lineage, it was confirmed by Nestin, MAP2 and Tuj1 markers expression. These iPSC derived neurons are able to produce A β oligomers, confirmed by Western Blot and immunostaining. With human iPSC derived neurons able to produce A β , we established an AD tridimensional cell culture model that will allow us the screening of molecules or compounds with therapeutic potential.

Disclosures: M.A. Hernandez-Sapiens: None. E.E. Reza-Zaldivar: None. R.R. Cevallos: None. Y.K.G. Gutierrez-Mercado: None. A.L. Marquez-Aguirre: None. K. Gazarian: None. A.A. Canales-Aguirre: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.27/P9

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

Support: NIH Grant R15NS091934

Title: Blood-brain barrier disruption increases amyloid-related pathology in a CAA mouse model

Authors: *I. ABDALLAH¹, A. KADDOUMI²

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Abstract: Functional blood-brain barrier (BBB) is important to maintain brain homeostasis. In Alzheimer's disease (AD), several studies reported the breakdown of the BBB with compromised tightness and function. Breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) are transport proteins localized at the luminal membrane of BBB and play important role in the clearance of amyloid beta (A β) from brain to blood. Also, the receptor for advanced glycation end products (RAGE) is known to interact with A β and mediates A β access to the brain across the BBB. The purpose of this study was to investigate the effect of pharmacological disruption of BBB on A β pathology. For this, elacridar was used as a model compound to disrupt the BBB function. Elacridar is an investigational compound known for its BCRP and P-gp inhibitory effect and widely used in cancer research. The CAA/AD mouse model TgSwDI (males, 4 months old) was used in the studies. Mice were divided to 2 groups (n=5/group), vehicle treated group as control and elacridar treated group. Elacridar was administered intraperitoneally (0.3 mg/kg/day) for 28 days. At the end of treatment, mice were

sacrificed for brains collection. Results showed that elacridar disrupted the BBB integrity as measured by increased IgG extravasation and reduced expression of tight junction proteins, increased amyloid deposition due to BCRP and P-gp downregulation and RAGE upregulation, and increased neuroinflammation. Further mechanistic studies revealed the effect was mediated by NF- κ B pathway activation. In conclusion, our results suggest that BBB disruption by inhibiting BCRP and P-gp exacerbate AD pathology in AD mouse model. In addition, our findings indicate that therapeutic drugs that inhibit BCRP and P-gp might increase the risk for AD.

Disclosures: I. Abdallah: None. A. Kaddoumi: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.28/P10

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

Support: NIH GRANT R01AG047928

Title: Assessment of astrocyte and microglia activation in a splicing-defective mouse model of Alzheimer's disease

Authors: *Y. JIAO, P.-C. CHEN, J. PENG

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Abstract: Alzheimer disease (AD) is the most common cause of dementia. The neuropathological hallmarks of Alzheimer disease are senile plaques and neurofibrillary tangles, along with glial cell activation and neuronal loss. In addition to amyloid hypothesis, we and collaborators have recently used a proteomics approach to identify in sporadic and familial AD cases, an early, tangle-like pathology of U1 small nuclear ribonucleic protein complex (snRNP), including U1-70K and its N-terminal cleavage product (N40K)¹⁻⁶. We have generated and characterized a transgenic mouse model by neuronal expression of N40K, which renders a dominant negative effect to downregulate full length U1-70K. The Tg animals recapitulate many AD-associated molecular events, including N40K insolubility, U1-70K loss and cytoplasmic mislocalization, and neuronal loss. Here we report a pilot histological analysis of N40K transgenic mice, including astrocyte or microglia activation during aging. The analysis shows in hippocampus astrocyte and microglia significantly increase in one-year-old N40K transgenic mice, compared with control littermates. The alteration of these glial cells is age-dependent, correlated with the degree of splicing deficiency. This study support that deregulation of splicing function can lead to glial activation and neurodegeneration, suggesting a potential role of splicing deficiency in AD pathogenesis. (This work is supported by NIH grants R01AG047928).

Disclosures: Y. Jiao: None. P. Chen: None. J. peng: None.

Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 046.29/P11

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

Title: Exercise and enriched environment are unable to prevent isolation stress-induced exacerbation of Alzheimer's pathology in 5xFAD mice

Authors: *J. L. PETERMAN¹, J. D. WHITE³, A. CALCAGNO¹, M. J. EIMERBRINK¹, C. HAGEN², G. W. BOEHM¹, M. J. CHUMLEY²

¹Psychology, ²Biol., Texas Christian Univ., Fort Worth, TX; ³Psychiatry, Yale Sch. of Med., New Haven, CT

Abstract: The prevalence of Alzheimer's disease (AD) continues to increase while its etiology remains elusive. Further, stress afflicts a considerable portion of the world's population, and, has similar effects to those of cardiovascular disease (CVD) and stroke, increasing disease risk and worsening disease outcomes. One such disease heavily impacted by stress is Alzheimer's disease. Indeed, stress has been found to exacerbate AD pathology in transgenic models of AD. We hypothesized that a social stressor, isolation stress, would increase the number of A β plaques in 5xFAD+ transgenic mice in comparison to group-housed controls. Further, we hypothesized that isolated animals would demonstrate a learning deficit in a contextual fear-conditioning (CFC) paradigm, a hippocampus-dependent memory task. Additionally, we sought to determine whether pathological or behavioral impacts of isolation stress could be prevented through exposure to exercise alone or to exercise and an enriched environment throughout the isolation period. Two-month-old 5xFAD+ and 5xFAD- animals were isolated or group housed for two and three months. An additional subset of 5xFAD+ mice were housed in isolation, housed in isolation with an exercise wheel, or housed in isolation with an exercise wheel as part of an enriched environment. After extended isolation or group housing, cognition was assessed utilizing CFC, and brain tissues then were removed and hippocampal plaque counts and A β levels were determined. Two and three months of isolation stress significantly increased the number of plaques in the hippocampus of 5xFAD+ mice. Isolated animals also displayed a significant cognitive deficit in CFC. The mechanisms are currently being explored. Further, exercise and an enriched environment were unable to prevent these isolation-induced effects. Understanding how stress impacts the onset and progression of AD is critical, as human populations continue to endure significant stress over the lifespan.

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Poster

046. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models I

Location: SDCC Halls B-H

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Program #/Poster #: 046.30/P12

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

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Title: TDP-43 interacts with mitochondrial proteins critical for mitophagy and mitochondrial dynamics

Authors: S. A. DAVIS¹, S. ITAMAN¹, C. KHALID-JANNEY¹, J. SHERARD¹, J. A. DOWELL², N. J. CAIRNS³, *M. A. GITCHO¹

¹Biol. Sci., Delaware State Univ., Dover, DE; ²Wisconsin Inst. for Discovery, Madison, WI;

³Neurol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Transactive response DNA-binding protein of 43kDa (TDP-43) functions as a heterogeneous nuclear ribonucleoprotein and is the major pathological protein in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). TDP-43 pathology may also be present as a comorbidity in approximately 20 to 50% of sporadic Alzheimer's disease cases. In a mouse model of MND, full-length TDP-43 increases association with the mitochondria and blocking the TDP-43/mitochondria interaction ameliorates motor dysfunction. Utilizing a proteomics screen, several mitochondrial TDP-43-interacting partners were identified, including voltage-gated anion channel 1 (VDAC1) and prohibitin 2 (PHB2), a crucial mitophagy receptor. Overexpression of TDP-43 led to an increase in PHB2 whereas TDP-43 knockdown reduced PHB2 expression in cells treated with carbonyl cyanide m-chlorophenylhydrazone (CCCP), an inducer of mitophagy. These results suggest that TDP-43 expression contributes to metabolism and mitochondrial function however we show no change in bioenergetics when TDP-43 is overexpressed and knocked down in HEK293T cells. Furthermore, the fusion protein mitofusin 2 (MFN2) interacts in complex with TDP-43 and selective expression of human TDP-43 in the hippocampus and cortex induced an age-dependent change in Mfn2 expression. Mitochondria morphology is altered in 9-month-old mice selectively expressing TDP-43 in an APP/PS1 background compared with APP/PS1 littermates. We further confirmed TDP-43 localization to the mitochondria using immunogold labeled TDP-43

transmission electron microscopy (TEM) and mitochondrial isolation methods. There was no increase in full-length TDP-43 localized to the mitochondria in APP/PS1 mice compared to wild-type (littermates); however, using C- and N-terminal-specific TDP-43 antibodies, the N-terminal (27kDa, N27) and C-terminal (30kDa, C30) fragments of TDP-43 are greatly enriched in mitochondrial fractions. In addition, when the mitochondrial peptidase (PMPCA) is overexpressed there is an increase in the N-terminal fragment (N27). These results suggest that TDP-43 processing may contribute to metabolism and mitochondrial function.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.01/P13

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

Support: This project was supported by funding from the EPFL

Title: Novel methodologies for reproducing pathological tau *in vitro*: A powerful platform for mechanistic studies, discovery of novel imaging agents and novel therapies for the treatment of Alzheimer's disease and tauopathies

Authors: *N. AÏT BOUZIAD¹, J. ADAMCIK², R. MEZZENGA², H. A. LASHUEL¹

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Abstract: Since the discovery and the successful production of recombinant Tau, efforts to reproduce the Tau pathology found in the post-mortem brain of Alzheimer's disease (AD) patients have focused on the use of polyanions to induce the formation of Tau aggregates. Although this approach does accelerate Tau aggregation, the aggregates formed under these conditions are polymorphic and bear no structural or morphological resemblance to the paired helical Tau aggregates found in AD brain (PHFs). Despite these limitations, many of the drug discovery efforts aimed at identifying inhibitors of PHFs formation and spreading of Tau pathology and to screen for imaging agents to monitor the progression of the AD still rely on aggregates derived from unmodified recombinant Tau. Although Tau aggregates can be isolated from AD brain, the quantities obtained are not sufficient for large-scale R&D programs. We have identified a novel Tau species that interacts with monomeric full-length Tau and templates efficiently its conversion into highly ordered helical filaments that bear striking structural and morphological properties of PHFs isolated from AD brains. The *in vitro* generated PHFs seed Tau aggregation in hippocampal and cortical primary neurons. It is noteworthy that

this is the first time ever that recombinant full-length Tau and Tau isoforms could be converted into PHFs-like structures in vitro. We believe that the development of small molecules and antibodies that target this species and interfere with its templating effects represent viable therapeutic strategies for preventing or slowing the progression of AD.

The structure of PHFs derived from AD brain was recently solved by Cryo-TEM and provided important insight into the structural basis of Tau aggregation and PHFs formation. While this represents an important advance, the use of brain-derived material is of limited utility in mechanistic studies aimed at elucidating the molecular and sequence determinants of PHFs formation and/or to understand the structural basis of PHFs heterogeneity in different Tauopathies. Our ability to reproduce this pathological form in the test tube in large amounts, combined with our ability to decorate these structures with different PTMs bring us closer to reproducing the various pathological forms of Tau and pave the way for developing effective therapies and imaging agents to enable monitoring AD progression.

Disclosures: **J. Adamcik:** None. **R. Mezzenga:** None. **H.A. Lashuel:** None.

Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.02/P14

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

Title: The study of axonal localization mechanisms of tau in neuron

Authors: ***M. IWATA**, S. WATANABE, T. MIYASAKA, H. MISONOU
Doshisha Univ., Kyotanabe-shi, Japan

Abstract: Tau is one of the microtubule-associated proteins (MAPs) in neurons and localizes specifically to neuronal axon, where it is thought to play important roles in polymerization and stabilization of microtubules. However, tau is accumulated in the soma and dendrites and forms neurofibrillary tangles in neurons affected in Tauopathies including Alzheimer's disease.

Therefore, it is speculated that the disruption of axonal localization causes the accumulation of tau and neurofibrillary tangles. However, the molecular mechanism of axonal localization of tau remains elusive. Therefore, we aim to elucidate how tau localizes to the axon. To study these problems, we began investigating the localization of human tau exogenously expressed in rat cultured neurons. However, exogenous tau was localized not only to the axon but the soma and dendrites, when tau was constitutively expressed from day 7 in culture, while endogenous tau localized properly to the axon in the same neurons. We then analyzed the expression and localization of endogenous tau in developing neurons and found that tau expression and axonal localization occur mostly during early development. Based on these results, we hypothesized that exogenous tau needs to be expressed in a similar pattern to that of endogenous tau during early

development. To establish this, we constructed a lentiviral vector, with which the expression of human tau can be controlled by an inducible promoter. Using this vector, we were able to express exogenous tau in early development and localize exogenous tau to the axon in cultured neurons. These results indicate that the expression pattern of tau is tightly controlled, and that aberrant expression of tau beyond early developmental stages leads to its mislocalization to the soma and dendrites. As exogenous tau can now be properly localized to the axon like endogenous tau in cultured neurons, we are trying to identify important regions for the axon specific localization and analyze the molecular behavior of tau in the axon.

Disclosures: M. Iwata: None. S. Watanabe: None. T. Miyasaka: None. H. Misonou: None.

Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.03/P15

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

Title: Tubulin degeneration induces tau abnormalities

Authors: *H. FUJIWARA¹, S. WATANABE², M. IWATA², M. NOBUHARA¹, S. WADAKAKUDA¹, H. MISONOU², T. MIYASAKA¹

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Abstract: Tauopathy is a type of neurodegenerative disorder including Alzheimer's disease defined by formation of tau filamentous inclusion in affected neurons. Tau is localized in axon and assumed to promote microtubule stabilization in healthy neurons. In contrast, hyperphosphorylated tau is accumulated at in somatodendrite of tauopathy neurons. Intriguingly, microtubules (tubulin) loss are also found in the neurons. Although it is believed that excessive phosphorylation of tau is involved in neurodegeneration, there is no direct evidence supporting this scenario. Conversely, previous reports suggest that microtubule degeneration may cause tau abnormality. The causal relationship betweenwith tau abnormalities and microtubule loss has been poorly understood. To investigate whether tubulin degeneration induces tau pathology, we performed a miRNA-mediated knock down system of tubulin-specific chaperon E (Tbce), an essential factor for the formation of alpha and beta tubulin heterodimeric complex, in mouse primary hippocampal neuron. The knock down of Tbce led to enhance localization of alpha-tubulin in cell body at DIV (days in vitro) 7, while that of acetylated- alpha- tubulin in the compartment was reduced. In these conditions, total tau and phospho-Ser202/Thr205 tau were increased in cell body without alteration of tau mRNA expression level. These indicates that the Tbce knock down induces not only reduction of active tubulin, which has the capability to polymerize microtubules, but also accumulation of phosphorylated tau in somata. These results

suggest that disruption of mechanism to maintain tubulin and/or microtubule properties promotes tau abnormalities that may lead tau pathology.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.04/Q1

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

Title: The identification of the tau C terminal sequences involved in aggregates formation

Authors: *S. SHIMONAKA¹, S.-E. MATSUMOTO³, Y. MOTOI¹, N. HATTORI²

¹Diagnosis, Prevention and Treatment of Dementia, ²Dept. of Neurol., Juntendo Univ., Bunkyo-ku, Japan; ³Dept. of Immunol., Kagoshima Univ., Kagoshima-shi, Japan

Abstract: <Introduction> Tau is known as a microtubule-associated protein but in pathological conditions such as Alzheimer's disease (AD), aggregated and abnormally phosphorylated forms of tau is deposited as neurofibrillary tangle (NFT) in neuronal cells. Thus far, numerous reports have indicated that C-terminal half of tau comprising 4-microtubule binding repeats plays a main role of tau filament formation. In this study, we sought which regions in C-terminal tau are mostly responsible for the tau aggregation using neuronal cell models. <Method> We constructed a series of partial deletion mutants of tau (Tau-Del 1-10) lacking 15-16 amino acid residues in 244-400. Tau mutants were transiently expressed in SH-SY5Y and those cells were treated with tau seeds including recombinant full length Tau (2N3R and 2N4R) and AD brain lysate. After 2-3 days incubation, cells were collected and tau aggregation was analysed by western blotting and fluorescent immunocytochemistry. Bacterially expressed 10 tau mutants were purified and used in *in vitro* aggregation assay and electron microscopic (EM) analysis. Synthetic peptides of targeted deletion sequences were prepared and their characteristics involved in tau aggregation were tested. To identify more accurate amino acid sequence, 3 partial deletion mutants (8-1: 353-358, 8-2: 358-363, 8-3: 363-368) inside Tau-Del 8 were prepared and analyzed. <Result> SH-SY5Y cells expressing Tau-Del 5 (306-321) and Tau-Del 8 (353-368), showed decreased aggregation propensity after adding both full-length tau and AD brain lysate, as seeds. EM analysis showed that Tau-Del 8 altered fibrous structure of aggregates to untypical entangled string-like form. Interestingly, Synthetic peptide (353-368) showed no *in vitro* aggregation ability, in contrast to peptide (306-321) which aggregated itself. Furthermore, we identified Tau-Del 8-2 (358-363) and Tau-Del 8-3 (363-368) as an aggregation responsible sequence. <Conclusion> We identified that sequences, 306-321, and 353-368 would play an important role in tau aggregation. 306-321 overlapped with previously reported PHF6 (306-311)

sequence but 353-368 has not been reported. 353-368 is a novel sequence which has no self-aggregation ability but involved in the formation of fibrous structure of tau aggregates.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.05/Q2

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

Support: RO1 AG054025
RO1 NS094557

Title: Modulating disease-relevant brain derived tau oligomeric strains by small molecules

Authors: *F. LO CASCIO^{1,2}, A. PALUMBO PICCIONELLO³, S. MCALLEN¹, A. ELLSWORTH¹, N. BHATT¹, R. KAYED¹

¹Neurol., Univ. of Texas Med. Br., Galveston, TX; ²Exptl. Biomedicine and Clin. Neurosciences, ³Biological, Chem. and Pharmaceut. Sci. and Technologies, Univ. of Palermo, Palermo, Italy

Abstract: Alzheimer's diseases (AD) is the most common age-related neurodegenerative disorder affecting millions of people worldwide. AD is one of over 18 different diseases known as tauopathies, characterized by the pathological aggregation and accumulation of tau. During the disease, tau detaches from the microtubules and undergoes conformational changes leading to the formation of different types of aggregates and inclusions including the widely-known neurofibrillary tangles (NFTs). Recent findings suggest that the smaller and soluble tau oligomers have been shown to be more toxic with more proficient seeding properties for the propagation of tau pathology as compared to the fibrillar tau. However, the structural and biological features of tau oligomers are still poorly understood due to their dynamic nature and conformational heterogeneity. Therefore, tau oligomers can be present in many conformations known as tau oligomeric strains. Importantly, different strains could explain how the aggregation and accumulation of tau causes many disorders and diverse phenotypes in different individuals within the same disease. In preclinical studies tau aggregates have been effectively targeted by immunotherapeutic approaches, aptamers and anti-sense oligonucleotides (ASO). The focus should be on finding small molecules able to convert toxic aggregates to less toxic structures or ones that can be more easily degraded by active cellular mechanisms. Therefore, using small molecules to deplete the disease-relevant structures could prevent the spread of tau pathology moving the tau field forward in the development of novel therapeutic approaches for tauopathies. Here, we used newly synthesized curcumin derivatives to modulate the aggregation pathways of disease-relevant tau oligomeric strains thus to reduce their toxicity. We performed biochemical

techniques, including direct ELISA, and Western Blot analyses as well as biophysical and cytotoxicity assays to characterize Brain-derived Tau oligomeric strains (BDTOs) in the absence and presence of curcumin derivatives. Our data suggest that novel curcumin derivatives modulate BDTOs aggregation pathways, resulting in the formation of tau structures with decreased toxicity as assessed in primary cortical neurons. These results may lead to the discovery of new compounds, effective against one or more tau strains. Finally, curcumin derivatives could contribute both in the development of novel therapeutic approaches for AD and other tauopathies as well as in diagnostic field as imaging agents able to detect toxic tau oligomers and differential diagnosis for tauopathies.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 047.06/Q3

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

Support: Alzheimer Nederland (WE.03-2016-05)

Title: The role of the endosomal system in tau pathology

Authors: ***S. VÁZQUEZ SÁNCHEZ**¹, **V. WIERSMA**¹, **W. SCHEPER**², **J. VAN WEERING**²
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder and the most common cause of dementia. AD is characterized by deposition of pathological tau and amyloid- β proteins, which both seem to spread through the brain in a defined pattern. Endosome trafficking genes are associated with AD and one of the first cellular symptoms observed in early AD brains is endosome swelling. Endosomes are essential organelles for protein degradation and recycling, including amyloid precursor protein (APP) and tau. While the link between endosome trafficking and amyloid- β production is becoming clear, the role of the endosomal system in tau pathology remains poorly understood. We hypothesize that aberrant endosomes play a key role in the development and spreading of tau pathology. We have characterized the role of endosome sorting pathways in tau aggregation in neuronal networks and assessed tau content of different compartments of the endosomal system. This study uncovers endosomal traffic pathways that might function as potential drug targets to prevent the spreading of tau pathology through the brain and thereby limit AD progression.

Disclosures: S. Vázquez Sánchez: None. V. Wiersma: None. W. Scheper: None. J. van Weering: None.

Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.07/Q4

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

Support: NIA RFO1, AG051538

Title: Bdnf reduction triggers aep-cleaved tau to bind and inhibit trkb receptors, mediating the pathogenesis of alzheimer's disease

Authors: *J. XIANG^{1,3}, Z.-H. WANG⁵, E. AHN⁵, X. LIU⁵, S.-P. YU⁵, F. P. MANFREDSSON⁶, I. M. SANDOVAL⁶, J.-Z. WANG⁷, S. WU⁴, K. YE²

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Abstract: BDNF and its cognate receptor TrkB play critical roles in synaptic plasticity and neuronal survival. Both are decreased in human brain during the aging process and in numerous neurodegenerative diseases. Declined BDNF levels associate with synaptic and neuronal loss and cognitive impairment with aging and Alzheimer's disease (AD), but there is little evidence showing that BDNF signaling would play a major role in the disease specific amyloid or tau pathology.

Most recently, we have reported that delta-secretase acts as an age-dependent asparagine endopeptidase (AEP), which cleaves Tau at N368 residue and promotes its aggregation and toxicity in AD (**Nature Medicine, 2014**). Moreover, we show that it also cleaves APP at both N373 and N585 sites in AD brains. The resultant truncate APP 586-695 is a much better substrate for BACE1 to generate more A β (**Nature Comm. 2015**). Inhibition of AEP in 5XFAD and Tau P301S mice by an orally bioactive and brain permeable small molecule exhibits promising therapeutic efficacy toward AD (**Nature Comm. 2017**). Together, these reports strongly support that delta-secretase is necessary for AD onset in various animal models. Our recent research indicates that BDNF deprivation triggers Tau proteolytic cleavage by AEP, and the resultant Tau N368 fragment binds TrkB receptors and blocks its neurotrophic signalings, inducing neuronal cell death. Knockout of BDNF provokes AEP activation and Tau N368 cleavage in BDNF f/f mice, inducing AD-like pathology and cognitive dysfunction, which can be restored by expression of the AEP-resistant Tau N255A/N368A mutant. Disrupting the association between Tau N368/TrkB by a small peptide or employing AEP-uncleavable Tau

N368A mutant, we show that AEP cleavage of Tau is indispensable for BDNF reduction-elicited pathologies. Further, treating Tau P301S and 3xTg mice with anti-Tau N368 antibody, we demonstrate that this immunotherapy successfully cleans up Tau pathologies and Abeta plaques, leading to upregulation of neurotrophic signalings and recovery of the cognitive functions in these AD animal models.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.08/Q5

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

Support: NIH Grant U54NS100717
NIH Grant 1R01AG054214
Tau Consortium
BrightFocus Foundation A2016360F
NIH Grant 1K01AG057862

Title: Mapping the activity-dependent tau interactome in human iPSC-derived neurons

Authors: *T. E. TRACY^{1,2}, D. SWANEY^{3,2}, M. MORITZ^{3,2}, M. WARD^{4,1,2}, R. HUTTENHAIN^{3,2}, S.-W. MIN^{1,2}, M. TELPOUKHOVSKAIA^{1,2}, J. MARTIN^{1,2}, C. WANG^{1,2}, P. D. SOHN^{1,2}, E. STEVENSON³, I. AVELLANO¹, Y. ZHOU¹, N. J. KROGAN^{3,2}, L. GAN^{1,2}
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Abstract: Tau accumulation in the brain is associated with toxicity and cognitive decline in neurodegenerative diseases including Alzheimer's disease. Tau interacts with the microtubule-based cytoskeleton, but little is known about what other tau-associated protein networks contribute to disease pathogenesis. During the progression of Alzheimer's disease, pathological tau spreads throughout the brain in a stereotypical pattern. Growing evidence suggests that tau spreads across synaptically connected neurons and neurons secrete tau in response to enhanced neuronal network activity. Activity-induced trans-neuronal tau propagation may involve the interaction of tau with a protein complex that regulates its active release from neurons. We developed an approach to investigate the tau interactome during its activity-induced release from cultured human iPSC-derived neurons. Human iPSC-derived glutamatergic neurons were engineered for the expression of tau fused with APEX, an ascorbate peroxidase that catalyzes the

biotinylation of proteins in close proximity upon a brief incubation with hydrogen peroxide. We used APEX proximity-dependent biotin labeling and mass spectrometry to quantify tau-associated proteins in neurons upon enhanced activity compared to neurons that were unstimulated. This approach enabled the identification of proteins that were significantly more associated with tau during enhanced neuronal activity. The activity-dependent tau-associated proteins identified in this study may facilitate tau release and spreading across neuronal circuits in neurodegenerative disease.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.09/Q6

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

Title: Interaction of rna-binding proteins musashi and tau oligomers in alzheimer 's disease

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Abstract: Many RNA-Binding Proteins (RBPs) accumulate and aggregate in different neurodegenerative disease, including Alzheimer's disease (AD). We discover that RBPs Musashi, a protein family that includes two members Musashi1 and Musashi2 (Msi1 and Mi2) which are known to be expressed in neuronal stem cells and overexpress in different type of cancers, are prone to aggregation, form toxic aggregate *in-vitro*, accumulate in AD human brains and strongly associated with tau protein. Previous studies, including ours, have shown that RBPs such as TDP-43 form toxic oligomers that interact with tau and potentially influence its toxicity in the neurons. The goal of this study is to investigate the potential role Msi proteins in neurodegenerative diseases. We studied Msi1 and Msi2 aggregation *in vitro*, the cellular localization in cell cultures and human brain tissues. Herein we found, for the first time, that both Musashi proteins aggregate *in-vitro* and form toxic oligomers and protofibrils. In addition, we discovered potential toxic interactions of Msi proteins aggregates with other disease associate proteins such as amyloid- β and tau. Moreover, preliminary analysis of AD and age-matched control brain tissues suggest changes in the expression, cellular localization and aggregation of

Musashi proteins. Our novel findings suggest that Msi proteins may play a role in cellular dysfunction and AD pathogenesis.

Disclosures: **M. Montalbano:** None. **U. Sengupta:** None. **S. McAllen:** None. **M.G. Kharas:** None. **R. Kayed:** None.

Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.10/Q7

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

Support: NIH RO1AG054025
NIH RO1NS094557
NIH RF1AG055771

Title: Generation and characterization of tau aggregates

Authors: ***A. ELLSWORTH**, G. GHAG, N. BHATT, U. SENGUPTA, R. KAYED
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Abstract: Tau aggregation is a hallmark of AD and many neurodegenerative diseases. It forms different stages of aggregates with different morphologies, including fibrillar oligomers, misfolded monomer, and others types of aggregates. However, recent studies suggest that each one of these species contain different conformationally distinct subgroups (strains). Work from our lab and others suggest that soluble, oligomeric forms of tau are likely the most toxic entities in diseases and can act as seeds to induce the misfolding of tau. Classically, oligomers are mainly prepared using monomer as starting material. Here we show that sonication, a well-established method for the preparation of protofibrils can be used to generate homogenous and stable oligomeric samples. Therefore, it is critical to optimize methods for the preparation of the different oligomeric structures in order to compare their toxicity and their seeding potency. This will allow us to better understand the roles of these distinct tau aggregates in the disease pathology in order to create targeted immunotherapies.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 047.11/Q8

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

Support: 1R01NS091329-01A1
T32 GM118292-01A1
AZ140097

Title: Epilepsy and tau pathology

Authors: ***R. A. CLOYD**^{1,2}, J. F. ABISAMBRA², B. N. SMITH²
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Abstract: Alzheimer's disease and related tauopathies are among the most significant health related challenges faced by the aging population. In addition to loss of cognitive function and changes in personality, patients with tauopathic conditions experience seizures at a rate higher than the general population. Studies have found changes in the brains of patients with temporal lobe epilepsy that resemble the pattern of tau pathology of Alzheimer's disease or chronic traumatic encephalopathy. Additionally, reduction of tau levels or tau phosphorylation reduces the frequency or duration of seizures in rodent epilepsy models. Although existing reports suggest a relationship between tau phosphorylation and development of seizures, the specific nature of this relationship remains unclear. We will use pilocarpine injection to induce status epilepticus and, eventually, epilepsy to clarify the relationship between tau phosphorylation and epileptiform activity. Studies are being done to determine the effect of induced epilepsy on tau state (levels and phosphorylation) by measuring phospho- and total tau levels via Western blots and immunohistochemical staining at various time points after induction of seizures. The amount and distribution of total and phosphorylated tau and the ratio between the tau species will be examined. We will also define the effect of pre-existing tau pathology on epileptogenesis. Tau pathology will be induced in mice by AAV-mediated introduction of 4R0N P301L tau and the latency to development of epilepsy and frequency of seizures will be assessed. Successful completion of this project will provide a better understanding of how seizure activity and tau pathology interact.

Disclosures: **R.A. Cloyd:** None. **J.F. Abisambra:** None. **B.N. Smith:** None.

Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 047.12/Q9

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

Support: G0F8516 N Odysseus
IWT 135043
AFI #10810

Title: A β -induced exaggeration of Alzheimer-related τ spreading is associated with prion protein

Authors: *L. GOMES¹, S. HIPPEL^{2,5}, A. RIJAL UPADHAYA², K. BALAKRISHNAN^{2,3}, M. KOPER¹, J. REICHWALD⁶, S. RABE⁶, R. VANDENBERGHE⁷, C. A. F. VON ARNIM⁴, M. STAUFENBIEL⁶, D. THAL^{1,8}

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Abstract: Extracellular deposition of the amyloid β -protein (A β) and intracellular accumulation of abnormal phosphorylated tau-protein (τ) represent the pathological hallmarks of Alzheimer's disease (AD). Although both lesions accumulate in parallel in the brain and it has been observed that the presence of both pathologies accelerates the progression of AD, it is not yet clear whether there is a link between A β and τ pathologies. Here, we crossed τ -transgenic mice (Tau58) with different A β -producing mouse models to elucidate how A β affects τ -pathology. Tau58 mice crossbred with transgenic mice that overexpress mutant (APP23) or wild type (APP51/16) APP lead to τ -accumulation in the CA1 sector of the hippocampus and in the frontal cortex of 6 months old mice (n = 5-6), prior to detection of A β plaques. However, Tau58 mice crossed with mice producing intracellular A β independent of APP processing (APP48), did not exhibit evident τ -pathology in CA1 suggesting that extracellular A β is required for exaggeration of τ -pathology spreading. Accordingly, elevated levels of soluble A β were observed in the mice secreting APP-derived A β (APP23xTau58 and APP51/16xTau58). Furthermore, co-localization of phosphorylated- τ and prion protein (PrP) was found in neurofibrillary tangles in these two mouse models. Immunoprecipitation confirmed an association of PrP not only with phosphorylated- τ but also with A β and APP CTF- α . A similar interaction between PrP, phosphorylated- τ and A β was observed in the human brain (n = 12 cases). This association was particularly noticed in advanced stage preclinical and symptomatic AD cases, suggesting that PrP may play a role in the progression of AD pathology. Based on these findings, we propose that PrP is a critical player in the interplay between A β and τ , specifically for the A β -related

spreading of τ -pathology. This presumed role of PrP in pathological conditions is consistent with the PrP-Fyn-related phosphorylation of τ and with PrP acting as a receptor for toxic protein species such as A β and α -synuclein.

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Poster

047. Alzheimer's Disease and Other Dementias: Tau: Biochemistry and Physiology

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 047.13/Q10

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

Title: Methylene blue inhibits formation of tau fibrils but not granular tau oligomers

Authors: M. SAITO¹, Y. SOEDA¹, S. MAEDA², *A. TAKASHIMA¹

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease, initially causing memory impairment and learning disorders, and eventually characterized by severe cognitive decline. The global rise in AD cases prioritizes the development of effective therapeutic for this condition. Both amyloid β (A β) and tau protein are causally linked to AD pathology, with deposits of extracellular A β contributing to the formation of senile plaques and intracellular accumulation of tau protein to neurofibrillary tangles (NFTs). To date, all A β -targeted therapeutic approaches have been unsuccessful, probably reflecting the fact that the number of NFT, rather than amounts of A β , correlate with neuronal loss. Accordingly, inhibitors of tau aggregation may offer a more promising therapeutic approach. Recently, methylene blue (MB), a compound already used clinically for other indications, emerged as a candidate and progressed to a Phase II clinical study as anti-AD compound. Unfortunately, the compound failed to halt the progression of dementia in mild-to-moderate probable AD patients. The latter prompted the

present analysis of the tau aggregation process during treatment with MB to gain insight into failure of the clinical study.

Our experiments were based on monitoring heparin-induced polymerization and aggregation of human wild-type human 2N4R recombinant tau (10 μ M) in the presence of MB (1, 10, 100 μ M), using the thioflavin T (ThT) fluorescence assay. Results showed decreased ThT fluorescence intensity in MB- versus vehicle-treated preparations. Since increased ThT fluorescence reflects binding to the β -sheet structure of tau, our finding suggests that MB inhibits the formation of β sheet-rich aggregates. However, inspection of the aggregates by atomic force microscopy (AFM) revealed that in fact, MB reduces the number of tau fibrils while increasing the number of granular tau oligomers. These findings were further confirmed at fractionation of tau aggregates by sucrose gradient centrifugation. Together, these results provide a plausible explanation for the poor success of MB in the latest clinical investigations: therapies should aim to inhibit tau granulation rather than to simply reduce tau fibril formation.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.01/Q11

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

Title: Development and validation of a tau seeding model in rTg4510 mice

Authors: B. MASTIS, R. CHANG, K. YANAMANDRA, B. DESROSIERS, T. FELDMAN, X. LANGLOIS, *T. DELLOVADE
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Abstract: To support the development of novel tau antibodies as potential therapeutics for Alzheimer's Disease (AD), a relatively fast, in vivo model of tau seeding has been developed. Human AD brain lysates were initially characterized using a quantitative cell based seeding assay and AD brain with the most competent seeds were used in this in vivo model. Human AD brain lysates were injected into the hippocampus of young tau rTg4510 mice at 8 weeks of age, prior to the onset of pathology. Three weeks post-injection, the level of "seeding" was measured by histological analysis of AT100 immunoreactivity (IR), in the ipsilateral hippocampal CA1 using paraffin histology. Initial studies demonstrated that either crude AD lysate or sarkosyl insoluble tau from AD brain resulted in about a 5 or 8 fold increase, respectively, of AT100 IR in the ipsilateral CA1 as compared to contralateral CA1 3 wks post-injection. In a time course study, mice were injected with AD lysate and euthanized 2, 7, 14 or 21 days post-injection. While the levels of AT100 IR were significantly elevated at the 14 day time point, IR was even further increased by 3 wks post-injection. To begin validating this model system, rTg4510 mice

(6.5 wks of age; n=13-15/group) were dosed twice weekly with either IgG or the phospho-tau mAb PHF1 for 3 prophylactic doses at 40 mg/kg, ip. Three days after the 3rd dose of antibody, AD brain lysate was injected into the hippocampus. Starting the following day, mice continued receiving twice weekly doses at 20 mg/kg, ip of either IgG or PHF1 for 3 additional weeks. Mice were then euthanized and the brains processed for paraffin histology. Image analysis of AT100 IR in the ipsilateral and contralateral CA1 revealed that prophylactic dosing with PHF1 significantly reduced AT100 IR in the ipsilateral CA1 by approximately 60% as compared to IgG treatment. Studies are ongoing to confirm and extend these initial model validation data to prepare for future in vivo screening of tau antibodies.

Disclosures: **B. Mastis:** A. Employment/Salary (full or part-time);; Abbvie. **R. Chang:** A. Employment/Salary (full or part-time);; Abbvie. **K. Yanamandra:** A. Employment/Salary (full or part-time);; Abbvie. **B. Desrosiers:** A. Employment/Salary (full or part-time);; Abbvie. **T. Feldman:** A. Employment/Salary (full or part-time);; Abbvie. **X. Langlois:** A. Employment/Salary (full or part-time);; Abbvie. **T. Dellovade:** A. Employment/Salary (full or part-time);; Abbvie, Inc.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.02/Q12

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Construction of a tau-seed injection model using hTau mice

Authors: ***B. HUTTER-PAIER**¹, **S. AKASOFU**², **J. GARTLON**³, **M. ROBERTS**³, **E. SAJEDI**⁴, **R. DE SILVA**⁴, **T. LOEFFLER**¹, **S. DULLER**¹

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Abstract: Introduction: When natively unfolded microtubule-associated protein tau assembles to highly structured tangles a tauopathy develops. Tauopathies are observed in neurodegenerative diseases such as Alzheimer's disease (AD) or frontotemporal dementia (FTD). The precise mechanism of tangle formation is not completely understood, but in recent years, evidence has accumulated that tauopathies can be induced by "seeding". Since most tau transgenic mouse models lack significant levels of insoluble tau or tangles, the development of tau-seeding models gained more and more attention.

Method: To generate a tau-seeding model with highest translational value, we used hTau transgenic mice as acceptor. Mice are bred on a murine tau knockout background, hence lacking endogenous tau. Additionally, hTau mice overexpress all human tau isoforms without mutations,

therefore coming closest to human conditions. Six months old hTau animals received a single unilateral intra-hippocampal injection of one of three different tau seeds: (1) recombinant P301S tau, (2) insoluble tau from rTg4510 mouse tissue or (3) insoluble tau from human AD brains was injected. Vehicle injected mice and non-injected mice served as controls. Three months after injection, the ipsi- and contralateral hippocampus and cortex were analyzed for changes in soluble and sarkosyl insoluble tau species.

Results: While soluble tau levels were not influenced by any application, sarkosyl insoluble tau significantly increased in the human AD injected hippocampus. Also in the ipsilateral cortex of female mice from this group (3), a significant increase in sarkosyl insoluble tau was detected. Even in the contralateral hippocampus a tendency to increased insoluble tau levels was observed by Western blot, which will be further investigated by immunosorbent assay.

Conclusion/Summary: Therefore, unilateral intra-hippocampal injection of insoluble tau from human AD brains into hTau mice represents a suitable model for further investigation of tau aggregation, seeding and spreading as well as associated interventions.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.03/Q13

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: TTBOF/29267
IWT140775

Title: Spatiotemporal profiling of tau pathology in a fibril-seeded mouse model with light-sheet microscopy

Authors: J. DETREZ¹, H. MAURIN², K. VAN KOLEN², R. WILLEMS², J. COLOMBELLI³, B. LECHAT⁴, B. ROUCOURT⁵, F. VAN LEUVEN⁶, S. BATOUT⁷, P. LARSEN², R. NUYDENS², *J.-P. TIMMERMANS¹, W. H. DE VOS^{1,8}

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Abstract: AD is characterised by a progressive accumulation of soluble amyloid beta and hyperphosphorylated tau (pTau) in the brain. Both proteins progressively spread throughout the

brain and the respective proteins are considered to seed further aggregation. To study spreading of pTAU, a mouse model (Tau.P301L) was studied by stereotactic inoculation of fibrils, either derived from synthetic tau-peptides (K18) or isolated from AD brains (ePHF), in the CA1 region. Spatiotemporal dynamics of tau pathology was analysed in iDISCO⁺-cleared whole brains by light-sheet microscopy, followed by image reconstruction, quantification and mapping to an anatomically annotated reference brain. pTau was visualised using an AT8 antibody. Non-injected Tau.P301L mice only started to accumulate significant amounts of tau at 6 months, predominantly in the brainstem. Inoculation of 3 months-old mice with K18 fibrils expedited tau pathology, with AT8-positive neurons emerging as early as 7 days post injection (DPI), in both hemispheres. The tauopathy pattern differed from that of control Tau.P301L mice with strong enrichment in hippocampus, cortex and thalamus, and only negligible proportions of tau pathology in the brainstem. The K18-induced spreading pattern followed the anatomical connections from the injection site. ePHF inoculation showed similar but slower progression, with negligible tau pathology at 28 DPI, but a pronounced AT8 load at 84 DPI, spatially resembling the K18 inoculation profile. This combined approach of targeted seeding and *in toto* pathology staging will allow evaluating the potential of therapeutic interventions aimed at halting or reversing the spreading process.

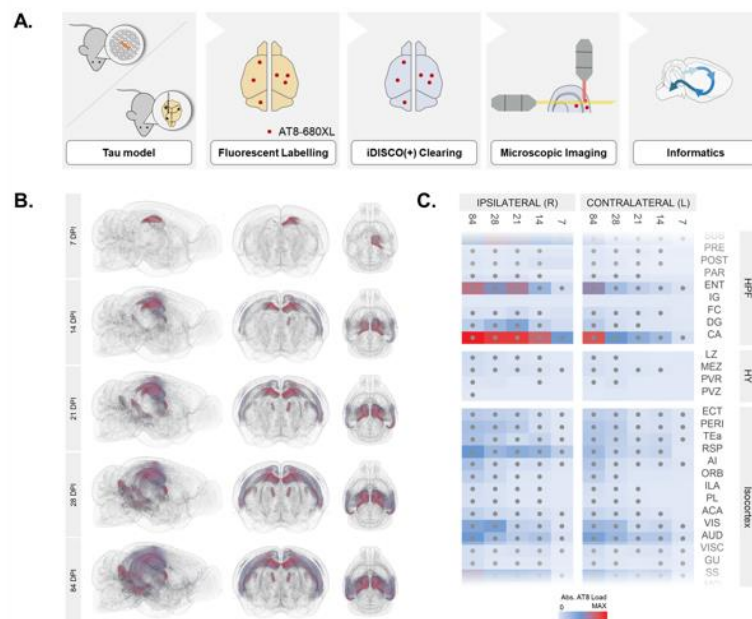


Figure 1: *In toto* imaging of hyperphosphorylated tau in P301L mice after K18 inoculation

A. Workflow for microscopic interrogation of tau pathology in intact brain. **B.** 3D rendering of AT8 pathology in K18-injected TAU.P301L mouse brains over time. **C.** Heatmap plots are used to visualise the AT8 load in brain subregions over time. P-values within the tiles indicate significant increases compared to buffer-injected controls.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.04/Q14

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH 1R21AG058080-01

Title: Prion-like tau seeds are aberrantly modified in neurons via inhibition of HDAC6

Authors: *J.-H. TSENG¹, T. J. COHEN²

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Abstract: The propagation of tau pathology in a prion-like manner via tau release and uptake could underlie a spectrum of distinct clinical syndromes including Alzheimer's disease (AD) and related tauopathies. While evidence indicates that tau seeds are readily taken up, it is unclear how they are processed. Here, we analyzed wild-type and disease-linked mutant tau fibrils to evaluate their mechanism(s) of pathogenicity. Unexpectedly, we show that P301L tau fibrils are aberrantly post-translationally modified within the microtubule-binding repeat domain (MTBR) via acetylation and phosphorylation, sediment in the heavy vesicular fraction, and localize to autophagosomes. We show that P301L fibrils are direct inhibitors of the deacetylase HDAC6, more so than wild-type fibrils, thus explaining their aberrant acetylation patterns. Surprisingly, we show that fibril interactions with endogenous soluble tau facilitates their acetylation. Once acetylated at residue K280, fibrils show a significant acceleration in aggregation and seeding propensity. Thus, tau seeds undergo distinct modifications, which could generate and propagate tau conformers in AD and other tauopathies. Dissecting tau modification profiles may provide valuable insights into the elusive structural and biological nature of transmissible tau species.

Disclosures: J. Tseng: None. T.J. Cohen: None.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.05/R1

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

Support: VLAIO (150882)
VLAIO (BM 140773)

Title: Evaluation of tau antibody epitope exposure in pathological seeds derived from tau transgenic mice and human brain

Authors: ***K. VAN KOLEN**¹, C. SOUSA¹, L. DELBROEK¹, A. MARREIRO^{1,2}, B. VASCONCELOS¹, M. VANDERMEEREN¹, C. THEUNIS¹, M. H. MERCKEN¹

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Abstract: Passive immunization with an anti-tau monoclonal antibody to block seeding by extracellular tau aggregates is currently explored as a disease-modifying strategy for the treatment of Alzheimer's disease (AD) and other tauopathies. As tau aggregates responsible for the spatio-temporal sequences of seeding events underlying disease progression are poorly defined, it is not yet clear which epitope is preferred for obtaining optimal therapeutic efficacy. Our internal tau antibody collection has been generated by immunizations with different tau species: aggregated- and non-aggregated tau and human *postmortem* AD brain-derived tau fibrils. In this communication, we describe and characterize a set of these anti-tau antibodies for their biochemical and biophysical properties, including binding assays and epitope mapping. Evaluation of the antibodies in cellular- and *in vivo* seeding assays revealed clear differences in maximal efficacy. Limited proteolysis experiments support the hypothesis that some epitopes are more exposed than others in the tau seeds. In particular for antibodies binding close to the tau microtubule-binding domain, efficacy seems to depend on the structural properties of fibrils purified from tau Tg mice- and *postmortem* human AD brain.

Disclosures: **K. Van Kolen:** A. Employment/Salary (full or part-time);; Janssen R&D. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Janssen R&D. **C. Sousa:** None. **L. Delbroek:** A. Employment/Salary (full or part-time);; Janssen PRD. **A. Marreiro:** None. **B. Vasconcelos:** None. **M. Vandermeeren:** A. Employment/Salary (full or part-time);; Janssen PRD. **C. Theunis:** A. Employment/Salary (full or part-time);; Janssen PRD. **M.H. Mercken:** A. Employment/Salary (full or part-time);; Janssen PRD.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.06/R2

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

Title: Modeling prion-like tau spread in *Drosophila melanogaster*

Authors: *S. A. LEVY¹, B. FROST²

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Abstract: Tauopathies are a class of neurodegenerative diseases characterized by the accumulation of fibrillar tau protein aggregates. In Alzheimer's disease, the most prevalent tauopathy, these aggregates form neurofibrillary tangles, one of the major pathological hallmarks of the disease. Strikingly, tau pathology propagates through the brain hierarchically over time and appears to spread along circuitry, suggestive of a prion-like cell-to-cell mode of tau spread. In recent years, increasing evidence has surfaced in support of this hypothesis. Tau is now known to spread between cells and form a variety of stably transmitted strains *in vitro* and *in vivo*. The cellular mechanisms mediating and regulating tau spread have not been well characterized. We are creating a *Drosophila melanogaster* model of the prion-like spread of pathogenic tau to provide a tool to study the processes involved in prion-like tau propagation in a short-lived, cost-effective animal model for which a variety of genetic tools are available. We employ a two-pronged approach to model two key features of prion-like protein transmission: 1) cell-to-cell spread of tau and 2) a capacity to recruit soluble tau into aggregates. Using native gel electrophoresis, we have determined that tau^{P301L}, a mutant associated with familial tauopathy, forms oligomers in *Drosophila* neurons *in vivo*, which suggests a capacity to seed aggregation. Based on this finding, tau^{P301L} was expressed in a subset of neurons and the spread of tau assessed by fluorescence *in situ* hybridization to detect tau mRNA combined with immunofluorescence to detect tau protein. Tau protein signal was found in cells lacking tau mRNA, indicating that tau spreads from cell to cell in *Drosophila*. A split-luciferase system will detect the capacity of spreading tau to seed aggregation of soluble tau in naïve neurons. Seed-competent tau^{P301L} fused to the C-terminal half of luciferase (Luc^N), will be expressed in one set of neurons, while wild-type tau fused to the C-terminal half of luciferase (Luc^C), will be expressed in another set of neurons synaptically connected to the first. Luc^N-labeled tau spreading along neuronal projections and recruiting soluble Luc^C-tagged tau into aggregates will emit a luminescence signal. A *Drosophila* model of tau spread will allow us to investigate the mechanisms controlling this phenomenon in adult brains, with the long-term goal of developing treatment strategies targeting the prion-like spread of pathogenic tau protein. In this context, a luminescence based model of tau seeding is well suited for screening of genetic and pharmacological interventions that interfere with putative transmission mechanisms.

Disclosures: S.A. Levy: None. B. Frost: None.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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

Support: NIH 1RF1AG054199-01

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AARF-16-442664

Title: Exosomes containing specific tau oligomer formations accelerate pathological tau phosphorylation in c57bl/6 mice

Authors: *Z. RUAN¹, A. YOSHII-KITAHARA¹, A. M. DELEO¹, S. IKEZU¹, S. VENKATESAN KALAVAI¹, R. KAYED², S. GORANTLA³, H. E. GENDELMAN³, T. IKEZU^{1,4}

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Abstract: Background: Increasing evidence suggests that tau aggregates spread and propagate via cell-to-cell transmission, by uptaking pathological tau and inducing misfolded aggregations of monomeric tau in recipient cells. A single intracerebral inoculation of extracellular vesicles containing tau into murine brains was shown to induce tau phosphorylation and soluble tau oligomer formation efficiently. Thus, we hypothesize that tau-containing exosomes derived from Alzheimer's disease patients' brains can serve as a seed for the spread of tauopathy in recipient animal brains. **Methods:** Exosome-enriched fractions were isolated from unfixed frozen human brain samples of Alzheimer's disease (AD) and control (CTRL) cases, as well as from the tau knockout (TKO) mouse brains. Tau oligomer epitopes were determined by dot blot using antibodies against T22, T18, TOMA1, TOMA2, TOMA3 and TOMA4 for all of the exosome fractions that were used as injectates. Two-month old C57BL/6 mice were inoculated with human brain exosomes containing tau, TKO exosomes, or saline, into the right dorsal hippocampus. After the injection, the brains were incubated for 18 weeks. The brains were then subjected to immunohistochemistry for phosphorylated-tau (p-tau) epitopes. **Results:** Each of the human-derived exosome samples has its own unique fingerprint of tau oligomer expression by dot blot. Surprisingly, mice that were injected with one of the AD and with one of the CTRL exosome samples showed remarkable AT8-immunoreactivity in the hilus and subgranular zone

regions of the hippocampus, while this was absent in the 9 other injectate groups including TKO-injected mice. Interestingly, one of these two positive exosome samples was only positive for TOMA2, while the other was positive for T22, T18 and TOMA3. **Conclusions:** Alzheimer's brain derived tau-exosomes accelerate pathological tau phosphorylation in relation to the specific type of tau oligomer(s) included within the exosomes.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.08/R4

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

Support: 2010N000157

Title: Selective partial decrease of GSK-3 beta reduces tau hyperphosphorylation, aggregation and propagation

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Abstract: Background: Glycogen synthase kinase 3 beta (GSK-3 β) is a pivotal kinase responsible for tau hyperphosphorylation in Alzheimer's disease (AD). It is aberrantly activated in human AD brains and AD mouse models. GSK-3 β overexpression causes tau hyperphosphorylation, synaptic and neuronal loss, inflammatory glial responses and memory deficits in mice. Aberrant activation of GSK-3 β in synapses may be a key event triggering abnormal accrual of hyperphosphorylated tau in synapses, and subsequent aggregation and propagation, ultimately leading to synaptic and neuronal anatomical collapse and cognitive impairment. **Goal:** To examine the therapeutic efficacy of selective partial inhibition of GSK-3 β to decrease/halt tau hyperphosphorylation, aggregation and propagation by targeting human tau expression in wild-type (WT) and hemi-knockout (HK) GSK-3 β backgrounds. **Methods:** We performed stereotactic injections of a viral AAV construct encoding for the fluorescent reporter protein eGFP and 4-repeat wild type human tau (4R-wt hTau) into the entorhinal cortex (EC) of

WT and GSK-3 β HK mice. After 12-week survival, brains were collected for histopathological and biochemical analyses. *In vitro* experiments using viral constructs encoding human WT Tau or P301L Tau in primary neurons derived from WT and GSK-3 β HK embryos were also conducted. **Results:** Partial selective GSK-3 β inhibition was safely achieved without significant neuronal loss in non-injected mice. Volume of EC injections and number of AAV-transduced neurons expressing hTau ("donor neurons") did not differ between WT and GSK-3 β HK mice. While levels of total hTau in synaptic and cytosolic compartments were comparable between WT and GSK-3 β mice, we detected a significantly higher accumulation of hyperphosphorylated tau (p-Tau) at synapses in WT mice. Quantification of AAV-transduced neurons expressing hTau ("donor neurons") and neurons receiving hTau through protein uptake ("recipient neurons") showed a significant decrease of tau propagation in GSK-3 β HK compared to WT mice. Parallel *in vitro* experiments using viral constructs encoding human wt Tau or P301L Tau in primary neurons derived from WT and GSK-3 β HK embryos further confirmed that selective partial decrease of GSK-3 β significantly reduced the formation of tau aggregates and tau propagation. **Conclusion:** Our results suggest that selective partial decrease of GSK-3 β represents an intervention that significantly modifies in *in vitro* and *in vivo* settings a tau initiated neurodegenerative cascade by significantly reducing aberrant accrual of hyperphosphorylated tau in synapses, and therefore tau aggregation and propagation.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.09/R5

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

Title: Viral-driven expression of a peptide tau aggregation inhibitor reduces neuropathological hallmark in a mouse model of tauopathy

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Abstract: Frontotemporal dementia and Alzheimer's disease (AD) are progressive neurodegenerative diseases characterized in part by aggregation of the tau protein. At the molecular and cellular levels aggregation of tau leads to a loss of normal tau function, the formation of toxic oligomers and neurofibrillary tangles (NFTs), initiates neurodegeneration and

a loss of connectivity, and results in cognitive decline. Tau aggregation is dependent on two highly aggregation-prone hexapeptide segments or "steric zippers"--VQIVYK and VQIINK--that are located in the repeat domains in the tau protein. ADRx has used a structure-based approach to design novel peptides that bind to these segments in their aggregation-competent conformation and has developed them into potent tau aggregation inhibitors (TAIs). Biochemically these TAIs completely block aggregation of multiple forms of tau, including the steric zippers, full-length human tau (hTau40), FTD-associated mutant tau (hTauP301L), and hyperphosphorylated hTau. In a luciferase-based hTauP301S reporter cell line TAIs linked to a cell-penetrating peptide to enable cell entry have also been shown to disrupt tau aggregation.

Here, we report an *in vivo* proof-of-concept experiment to test whether these novel TAIs can alter the course of pathological changes in a mouse model of neurodegeneration—the hTau40 P301L transgenic mouse rTg4510. Similar to humans with tauopathies, these mice develop tau deposition in neurons (oligomers and NFT-like fibrils), neurodegeneration, neuroinflammation, cognitive deficits, and behavioral abnormalities. To deliver the L-amino acid TAIs into the brains of rTg4510 mice, we have utilized the engineered adeno-associated viral vector AAV.PHP.B to deliver DNA encoding a TAI peptide throughout the brain. We have demonstrated that viral vector delivery can initiate TAI synthesis directly within the first-affected tau-expressing neurons of the transgenic mice, prior to the onset of observed pathology.

Aggregated tau quantified by anti-MC1 immunohistochemistry and quantitative PCR transcript analysis of hTau and expressed GFP and TAI will be presented. Results from this study enhance our understanding of aggregation-prone segments of tau as a therapeutic target and of TAIs as a potential therapy for AD and other tauopathies.

Disclosures: **A.P. Wright:** A. Employment/Salary (full or part-time);; ADRx. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds);; ADRx. **I. Hernandez:** None. **G. Luna:** None. **J. Scherrer:** A. Employment/Salary (full or part-time);; ADRx. **G. Naumann:** A. Employment/Salary (full or part-time);; ADRx. **Y.E. Sibih:** None. **M.I. Apostol:** A. Employment/Salary (full or part-time);; ADRx. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds);; ADRx. **B.E. Deverman:** None. **K.S. Kosik:** None. **J.J. Treanor:** None.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.10/R6

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

Support: Alzheimer's Association NIRG-396905
NHMRC 1105284

Title: The effect of human mutant tau on cognition and sleep in the rTg4510 mouse model of tauopathy

Authors: *R. J. KEENAN¹, H. DAYKIN^{1,2}, D. K. WRIGHT³, K. J. BARNHAM², G. ALLOCCA^{1,2}, D. HOYER^{1,2,4}, L. H. JACOBSON^{2,1}

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Abstract: Alzheimer's disease (AD) and frontotemporal dementia (FTD) are neurodegenerative disorders with a pathogenesis related to the development of pathological tau aggregates. Tau pathology correlates well with dementia symptoms in AD, therefore anti-tau therapeutics are currently under development for AD, and may also benefit other tauopathies such as FTD. Tau transgenic (Tg) rTg4510 mice contain the human P301L *MAPT* mutation associated with FTD, which is suppressible by administration of the tetracycline analog doxycycline (DOX). rTg4510 mice develop age-dependent cognitive deficits, however very few studies have examined the reversibility of deficits in different cognitive domains. We therefore used rTg4510 mice to assess whether genetically reducing tau accumulation with DOX affects performance in the Barnes maze, a spatial memory task less aversive than the Morris water maze. The Barnes maze includes readouts such as search strategy, in addition to acquisition and recall of spatial memory. As sleep disruptions are emerging as crucial aspects of these disorders, sleep-wake EEG/EMG recordings were also performed.

4.5-month-old male and female WT and Tg rTg4510 mice were administered a diet containing 200 ppm DOX or a control diet (CON) for 6 weeks (n = 16-19 per group). EEG/EMG head-mounts were surgically implanted and sleep was recorded over three consecutive days at 6 months of age. Cognition was assessed in the Barnes maze before brain samples were collected. A satellite group of male mice (n = 3-4 per group) did not undergo EEG/EMG surgery, but brains were assessed by *ex vivo* MRI scanning.

DOX only partially reversed acquisition deficits of Tg mice in the Barnes maze, but completely reversed recall deficits in the probe trial to a performance equal to that of WT mice. An increased spatial search strategy during acquisition trials was also observed in DOX-Tg versus CON-Tg mice. Work is in progress to define the sleep architecture of the rTg4510 mice relative to cognitive performance and to elucidate the effect of manipulating pathological tau accumulation on sleep. Western blot and MRI will determine the effects of DOX on tau burden and brain atrophy respectively, relative to cognitive and sleep parameters.

In summary, reduction of tau instigated soon after the initiation of accumulation of tau pathology reversed some, but not all, specific cognitive deficits in Tg rTg4510 mice. These data may help to define the range of responses available to anti-tau therapeutics and provide information regarding the influence that pathological tau accumulation has on the disruption of cognition and sleep in the rTg4510 mouse model of tauopathy.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.11/R7

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

Support: Alzheimer's Association 2016-NIRG-396905
NHMRC Australian Government: Project Grant 1105284

Title: Tau null mutation increases reward motivation but does not impair cognitive flexibility in mice

Authors: *S. OBERRAUCH^{1,2}, M. BRIAN^{1,2}, J. METHA^{1,2}, S. A. BARNES³, C. MURAWSKI¹, P. BOSSAERTS^{1,2}, C. NOWELL⁴, L. M. CHALLIS², A. J. LAWRENCE², T. J. FEATHERBY², D. HOYER^{1,2,5}, L. H. JACOBSON^{2,1}

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Abstract: Alzheimer's disease (AD), the most common form of dementia, and frontotemporal dementia (FTD) are characterized by an aberrant hyperphosphorylation of the scaffolding protein tau. With the progression of AD, tau pathology spreads in a reasonably orderly fashion across the brain, initially involving subcortical regions such as those associated with vigilance and reward, before progressing to cortical regions. Consequently, tau pathology is associated with cognitive decline, sleep and reward disruptions. With regard to the latter, subjects with AD and FTD exhibit less advantageous decision-making in reward-related tasks. Additionally, abnormal eating behaviours are a noted feature of FTD, particularly heightened impulsivity and the increased intake of sweet foods.

Tau hyperphosphorylation has been proposed to represent a loss-of-function modification. Furthermore, we have observed that mice deficient in tau are obese and hyperphagic. We therefore tested adult male and female tau-knockout (Tau-KO, n = 15) and wildtype (WT, n = 15) mice on a C57BL/6 background strain (i) for their motivation for saccharin reward, using a progressive ratio protocol and (ii) their cognitive flexibility in a reversal and probabilistic reversal learning task. Twenty-four hour baseline food intake and body weights were also assessed.

Tau-KO mice ate and weighed more than WT mice. Furthermore, Tau-KO mice showed increased motivation for effortful reward in the progressive ratio task, reaching approximately twice the breakpoint of WT mice. Tau-KO mice, however, did not show overt impairments in the ability to learn the tasks requiring cognitive flexibility compared to WT mice.

These data indicate that the loss of tau protein is associated with enhanced reward motivation.

This may also explain the over-eating and weight-gain phenotype of the tau-KO mutant. These findings may have implications for understanding both altered reward-related decision making in AD or FTD, and the targeting of tau protein as a therapeutic strategy for these disorders.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.12/R8

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

Support: FIS/IMSS/PROT/G17-2/754

Title: Arginine levels in 3xTgAD mice and its implication in cognitive deficit

Authors: ***K. L. MARTINEZ-GONZALEZ**^{1,2}, **P. GARCÍA**³, **L. SERRANO**³, **S. FLORES**³
¹Univ. Nacional Autonoma De Mexico, Mexico, Mexico; ²Posgrado en Ciencias Biologicas, Mexico, Mexico; ³Inst. Mexicano del Seguro Social, Mexico, Mexico

Abstract: Alzheimer's disease (AD) is a neurological disorder defined by progressive & irreversible neurodegeneration of the central nervous system & is the most common cause of dementia in elders. This disease leads to a gradual decline of cognitive function manifested by memory impairment. The synaptic deregulation starts in the hippocampus & eventually leads to neuronal loss & cognitive impairment, this is mainly due to structural changes involving the accumulation of neuritic β -amyloid plaques & neurofibrillary tangles of the hyperphosphorylated tau protein. In addition to the neuronal injury, new evidence suggests the involvement of the arginine metabolism in AD pathogenesis. L-arginine is a semi-essential amino acid that can be metabolized to form a number of bioactive molecules. Nitric oxide is a gaseous signaling molecule produced by NO synthase (NOS). NO derived from neuronal NOS plays an important role in synaptic plasticity & learning & memory, whereas endothelial NOS (eNOS)-derived NO is a key factor for the stabilization & regulation of the vascular microenvironment. In AD brains, NFTs & SPs are associated with reduce capillary expression of eNOS. Previous research has reported decreased arginine levels in AD brains. Hence, the study of changes in arginine levels in a 3xTg-AD mouse model allowed us to establish a parameter inside AD & define a possible relation between levels of arginine & cognitive deficit. We measured arginine levels by UPLC in cerebrospinal fluid (CSF) & brain tissue. Spatial memory was evaluated to define the behavioral deficit of each group. We found differences in arginine levels between between 3xTg-AD & WT groups at 8 and 12 months. This changes could be due to altered arginase I & arginase II

messenger RNA (mRNA) expression previously reported in tissue. Administration of an arginine precursor, allowed us to elevate levels in CSF & brain tissue in 3xTG-AD mice.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.13/R9

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

Support: NIH grants R01 NS077239
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Title: Abnormal cortical calcium activity in a tauopathy transgenic mouse model

Authors: *Q. WU^{1,2}, B. YANG³, W. LI³, Y. LIN^{1,2}, W. GAN^{1,2,3}, E. M. SIGURDSSON^{1,2,4}
¹Dept. of Neurosci. and Physiol., ²Neurosci. Inst., ³Skirball Inst., ⁴Dept. of Psychiatry, New York Univ. Sch. of Med., New York, NY

Abstract: Abnormal neuronal calcium activity is thought to be associated with Alzheimer's disease (AD), and has been detected in several APP mutant mouse models. It has not been thoroughly studied in tauopathy models. Here, we used in vivo two-photon imaging to examine calcium activity in cortical motor neurons in the JNPL3 tauopathy mouse model and age-matched wild-type mice of the same strain background. AAV-GCaMP6 viral construct was injected into the primary motor cortex (female, 9-10 months), for expressing the calcium indicator in Layer II/III pyramidal neurons, 28 days before two-photon imaging. Neuronal somatic calcium activity was analyzed in animals during resting or running on a treadmill (n = 577 neurons per group from 8 mice of each model). Compared to controls, the tauopathy mice had abnormal calcium activity with lower peak amplitudes of calcium transits (0.89 ± 0.03 (SEM) vs 0.82 ± 0.03 during resting, $p = 0.03$, and 1.09 ± 0.03 vs 0.89 ± 0.03 during running, $p < 0.001$), and higher number of calcium transits (5.86 ± 0.16 vs 7.75 ± 0.22 during resting and 8.05 ± 0.19 vs 10.41 ± 0.27 during running, $p < 0.0001$ for both). These functional deficits may potentially be attenuated or reversed with various tau-targeting therapies. In particular, tau immunotherapies are a promising approach for AD and related tauopathies. Eight such clinical trials are ongoing despite relatively limited knowledge of the potential mechanisms involved. Findings by us and others suggest that various pathways may be involved and the importance of each may depend on the antibody. A better understanding of the mechanism of action of tau antibodies in animal models will improve their selection for future clinical trials. We are currently examining the efficacy of tau antibodies in reversing neuronal tauopathy-associated

calcium abnormalities. Such functional assessment, in which each animal serves as its own control, will provide valuable insight into the mechanisms of tau immunotherapies and facilitate selection of antibodies for clinical trials.

Disclosures: **Q. Wu:** None. **B. Yang:** None. **W. Li:** None. **Y. Lin:** None. **W. Gan:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapy and related diagnostics that are assigned to New York University. Some of this technology is licensed to and is being co-developed with H. Lundbeck A.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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The Virginia Chapter of the Lady's Auxiliary of the Fraternal Order of Eagles (GSB)

Title: Characterization of a tau FRET biosensor sensitive to tau intramolecular folding

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Abstract: Abnormal tau folding and aggregation of the microtubule-associated protein, tau, is a hallmark of several neurodegenerative disorders, including Alzheimer's Disease (AD.) Tau is thought to maintain a paperclip-like folded conformation while bound to microtubules, but this conformation can be altered by phosphorylation, which may precede tau oligomerization and filament formation. While there are many ways to monitor tau aggregation, monitoring changes in folding is not well established. Using full length tau doubly labeled with the Förster resonance energy transfer (FRET) compatible fluorescent proteins, Venus and Teal, on the N and C termini, respectively, intensity and lifetime FRET can distinguish between a folded and unfolded conformation of tau in living cells independently of tau-tau intermolecular interactions. When expression levels are restricted to a low level in which intermolecular FRET contamination is minimized, Venus-tau-Teal is sensitive to microtubule binding state and phosphorylation in live

cells. When perturbed under conditions which disrupt the paperclip conformation of tau, an unfolding pattern in which the N and C termini move further apart is seen via an increase in donor lifetime. This tau biosensor and method of analysis can be used to evaluate perturbations to tau and may have promise as a diagnostic tool for detecting early indicators of disease development.

Disclosures: L. Saunders: None. H. Wallrabe: None. Z. Svindrych: None. A. Periasamy: None. G.S. Bloom: None.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.15/R11

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

Support: European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 676144 (Synaptic Dysfunction in Alzheimer Disease, SyDAD)

Title: The roles of physiological and pathophysiological tau in synaptic function and morphology

Authors: *M. ALBINO MATIAS¹, L. RAEYMAEKERS¹, C. WINTMOLDERS¹, A. BOTTELBERGS¹, W. DRINKENBURG¹, J. DE WIT², J. D. PITA-ALMENAR¹

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Abstract: Although the incidence of Alzheimer's disease (AD) keeps rising, our knowledge about its etiology is still incomplete. It is widely established that hyperphosphorylated tau is a key hallmark of the disease and that spreading of phosphorylated tau and deposition of neurofibrillary tangles is linked to the onset and progression of AD. However, the mechanisms by which tau hyperphosphorylation leads to synaptic dysfunction and morphological alterations remains unclear.

In this study we aimed to investigate the impact of tau hyperphosphorylation on the hippocampal circuit by using a tauopathy mouse model (TauP301L) in which tau pathology was triggered by injecting "tau seeds" in the hippocampus (Peeraer et al., 2015). Briefly, at 3 months of age, both male and female TauP301L mice were injected with fibrillized tau fragments in CA1 of dorsal hippocampus and 1 month later we performed whole-cell patch-clamp recordings of CA1 pyramidal neurons in acute slices of ventral hippocampus to assess their functional properties. Subsequently, neurons were reconstructed and stained with AT8 Ab to correlate their phosphorylated tau content with functional deficits.

Our preliminary results suggest that AT8 negative neurons have unaltered intrinsic properties regardless of the overall stage of tau pathology in the neighbouring neurons. However, from our data it is still not clear whether the presence of low levels of pTau affects excitability of neurons. On the other hand, we observed an increased frequency of spontaneous and miniature synaptic events on the AT8 negative neurons of the seeded mice, when compared to WT, non-injected, or buffer-injected age-matched controls. This increase in sEPSCs in the seeded model was not accompanied by changes in amplitude of synaptic currents indicating that changes such as increasing excitability are occurring in a subgroup of pre-synaptic neurons.

To identify the source of this pre-synaptic effect, we are currently studying the impact of pTau on the main excitatory inputs into the CA1, the Schaffer collaterals and Perforant pathways originated at CA3 and Entorhinal Cortex respectively. In addition, we are exploring whether inhibition is affected in the hippocampal circuitry after spreading of Tau pathology as it may play a role in the hyperexcitation we observed.

This study will allow us to investigate the correlation between spreading of tau pathology and the alteration of functional properties of neurons in local microcircuits. Gaining further knowledge in this matter will potentially help with the identification of new targets to modulate synaptic transmission/plasticity and counteract the synaptic deficits observed.

Disclosures: **M. Albino Matias:** A. Employment/Salary (full or part-time);; Janssen Pharmaceutica NV. **L. Raeymaekers:** A. Employment/Salary (full or part-time);; Janssen Pharmaceutica NV. **C. Wintolders:** A. Employment/Salary (full or part-time);; Janssen Pharmaceutica NV. **A. Bottelbergs:** A. Employment/Salary (full or part-time);; Janssen Pharmaceutica NV. **W. Drinkenburg:** A. Employment/Salary (full or part-time);; Janssen Pharmaceutica NV. **J. De Wit:** None. **J.D. Pita-Almenar:** A. Employment/Salary (full or part-time);; Janssen Pharmaceutica NV.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.16/R12

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

Support: Memorial University Dean's Innovation Fund
Seed, Bridge Fund to QY, CH, GM.

Title: A rat model of pretangle Alzheimer's disease featuring hyperphosphorylated tau in the locus coeruleus

Authors: ***A. GHOSH**¹, **S. TORRAVILLE**¹, **E. A. CHIRINOS**¹, **B. MUKHERJEE**¹, **F. M. MCCARTHY**¹, **S. MILWAY**², **S. WALLING**², **G. M. MARTIN**², **C. W. HARLEY**², **Q. YUAN**¹

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Abstract: The brainstem locus coeruleus (LC), which produces norepinephrine (NE), has been identified as a key structure in Alzheimer's disease (AD) development. Braak and Del Tridici propose that soluble hyperphosphorylated tau originating in the LC constitutes the beginning of AD, which can begin in childhood or puberty. Hyperphosphorylated tau then spreads to other neuromodulatory centers, finally appearing in trans-entorhinal cortex. This sequence constitutes Braak's new pretangle AD stages. The time course of pretangle stage transitions is variable, but can last decades. Later, hyperphosphorylated tau conversion to neurofibrillary tangles in trans-entorhinal cortex signals the start of Braak stages I-VI with tangles ultimately spreading throughout cortex. LC fiber degeneration, LC volume, and changes in LC mRNA synthesis correlate with AD tangle stages and with cognitive function, but LC cell loss is not observed until mid-stage AD. Changes in the LC and in LC-mediated cognitive function may index prodromal AD and represent a window for interventions.

We have created a rat model of prodromal AD by introducing a human pseudophosphorylated tau (htauE14) into the LC of TH-CRE rats. E14 represents 14 phosphorylation sites on tau protein that are phosphorylated in the prodromal stages of AD. We infuse AAV9-rEF1a-DIO-EGFP-htauE14 into the LC of 2-3 month-old rats, mimicking the onset of tauopathy during puberty in humans. We then assess performance in a similar odor discrimination task that depends on LC-NE support, followed by immunohistochemistry at various times. Preliminary results show that 8 months post-infusion, rats demonstrate impaired similar odor discrimination learning, while they perform comparably to control rats on dissimilar odor discrimination. EGFP+ cells were observed in the LC and EGFP had spread to mid-line subcortical nuclei by this time point. There was no LC cell loss, however, degenerated LC axon terminals in piriform cortex were indexed by reductions in NET density and by compensatory up-regulation of β -adrenoceptors. No tangles were observed using Gallyas staining. This mimics the early pretangle stages defined for human AD and indicates LC axonal function and LC-dependent difficult pattern discriminations may be compromised in prodromal AD.

Disclosures: A. Ghosh: None. S. Torraville: None. E.A. Chirinos: None. B. Mukherjee: None. F.M. McCarthy: None. S. Milway: None. S. Walling: None. G.M. Martin: None. C.W. Harley: None. Q. Yuan: None.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 048.17/R13

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

Title: Histological demonstration of plaques and tangles in brains of human Alzheimer's disease (AD) patients and parenchymal plaques in two rodent models of Alzheimer's disease: Usefulness of Styrelbenzine analog- FSB

Authors: *S. SARKAR¹, K. SAMBAMURTI², J. RAYMICK¹, J. HANIG³

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Abstract: Although several histochemical markers for amyloid plaques (SP) and neurofibrillary tangles (NFTs) have been synthesized since the discovery of plaques in the Alzheimer disease (AD) have shown to stain both plaques and neurofibrillary tangles in the human brain. Despite discovery of its ability to stain both SP and NFT over 13 years ago, the styrylbenzene derivative, (E,E)-1-fluoro-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (FSB), has only recently gained attention, primarily due to its ability to function as a contrasting agent for MRI imaging of AD pathology in vivo. The structure of the compound is a nuclide with quantized angular momentum, which explains its value as a contrast agent. In the current study, modification of the staining procedure showed tremendous improvement in the labeling of plaques and tangles in the human brain. Moreover, two rodent models of AD also used to show its value in labeling multiple lesions. Furthermore, our current modification allows us to detect SP in rodent in 15 minutes and both SP and NFT in human brains within 20 minutes. The study presents optimization protocols, in which, various parameters have been chosen to show how section thickness, use of frozen versus paraffin-embedded sections and selection of staining. Media can affect the intensity of the plaques and tangles in the brain. To determine the target of FSB potentially binds to, we have performed double immunolabeling of FSB with mOC64 (a conformational antibody that label A β 1-42) and results showed that all the plaques in the brain co-localized with mOC64 suggesting that FSB has the potential to bind all the A β containing plaques, making it a very sensitive detector of multiple forms of SP. Additionally, we found that phosphorylated-Tau antibodies (PHF1, CP13, AT8, TNT1, TNT2, S214), stains of NFT's stains failed to completely to co-localize with FSB, even though and none of those phosphorylated Tau has shown complete co-localization suggests that FSB is a unique tracer that has the potential to label both plaques and tangles. FSB is a rapid stain that is brighter with an ability with an ability to detect a larger range of pathologies that the popularity used stains to date. It also binds NFT at a distinct site shared by phosho-Tau antibodies and other stains define a novel target for evaluation of AD pathology.

Disclosures: K. Sambamurti: None. J. Raymick: None. J. Hanig: None.

Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.18/R14

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

Support: CIHR Grant 201610PJT -376978

Title: Alzheimer's disease-like hyperphosphorylation and conformational change of human tau protein following long-term overexpression in the rat locus coeruleus

Authors: *H. HALL¹, L. BREUILLAUD¹, L. FLORES AGUILAR², A. CUELLO¹

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Abstract: Degeneration of noradrenergic neurons of the locus coeruleus (LC) is present at advanced stages of Alzheimer's disease (AD), and is accompanied by reduced cortical and hippocampal noradrenaline (NA) levels. There is also concomitant evidence that this system is impaired at earlier stages of the disease. In particular, it is suggested that the LC may be an initial site of tau deposition. This would suggest that the LC may have a key role in the early AD pathogenesis. Unfortunately, the AD-like early accumulation of tau in the LC is not replicated by transgenic AD models. To address this, we generated rats overexpressing human tau in the LC using somatic transgenesis.

Recombinant adeno-associated viral vectors (AAV9) designed to express either human wild-type tau, P301S mutant tau, or GFP under the control of the synthetic dopamine beta hydroxylase promoter PRSx8 (to selectively target transgene expression to NA neurons) were injected in the LC of young (3 month-old) Wistar rats. After a year, rats were sacrificed and their brains processed for immunohistochemical analyses.

NA neurons were stably transduced by the transgene throughout the LC, 12 months after injection. Widespread GFP immunoreactivity was observed in fiber terminals of target regions, including hippocampus and neocortex, and seen ascending from LC neurons through the dorsal noradrenergic bundle. AT8 and AT180 immunoreactivity revealed hyperphosphorylated tau in the LC, while MC1 immunoreactivity identified tau conformational change as seen before the assembly of paired helical filaments in the brain of AD patients. Pathological changes were observed following overexpression of both wild-type and mutant tau, without apparent cell loss. After one year of transgene expression, microglia appeared to be in a resting state in LC projection areas (hippocampus and neocortex).

In summary, viral-vector mediated delivery of human tau protein into the LC of rats leads to stable protein expression and pathological changes as seen in human AD brains. This model may help to further elucidate the consequences of an early LC demise on the evolution of the AD pathology.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.19/R15

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

Support: 1R15AG023604-01
5R01ES015867-03

Title: Tau and alpha-synuclein in lead exposure model of neurodegeneration

Authors: *S. W. BIHAQI¹, B. ALANSI, 02881², A. LAHOUEL³, M. ANWAR⁴, F. MUSHTAQ², M. DASH², N. H. ZAWIA, 02881²

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Abstract: The accumulation of α -synuclein (α -Syn) aggregates is a hallmark of Parkinson's disease, synucleinopathies and accumulations of tau aggregates are found in the individuals with dementia; referred to as tauopathies. Accumulating evidence has indicated an overlap between synucleinopathies and tauopathies, suggesting a link between these proteinopathies. Moreover, the sporadic nature of the majority cases of neurodegenerative diseases argues for an environmental link that may drive their pathogenesis. Published reports from our lab showed that lead (Pb) exposure occurring during brain development pre-determined the expression and regulation of tau gene and pathology. Recently, we showed that developmental Pb exposure results in cognitive decline but did not change the expression of the amyloid pathway in the absence of tau (Kelsey et al. 2018). Thus, in order to examine the relationship between these proteinopathies and their connection to cognitive performance, we studied the changes in the α -Syn pathways in transgenic mice lacking the tau gene. Pb induced alteration in gene expression was also examined by an *in-vitro* model involving differentiated SHSY5Y human neuroblastoma cells. The cells were exposed to a series of Pb concentrations for 48 h and allowed to persist for a week in-order to mimic the latent impact on the expressions of α -Syn and intermediates involved in the pathway. Our results indicated early life Pb exposure was accompanied by latent up-regulation in α -Syn in these mice. Furthermore, prior exposure to Pb *in-vitro*, also results in an increase in α -Syn, its phosphorylated forms, as well as increase in GSK-3 β and caspase-3. Thus, suggesting that an environmental agent can act as a latent inducer of both α -Syn and associated kinases that are involved in tau hyperphosphorylation and allude to the interactive nature between these two neurodegenerative pathways.

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Poster

048. Alzheimer's Disease and Other Dementias: Tau: Animal and Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 048.20/R16

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

Support: VLAIO Baekeland HBC.2016.0219

Title: Development of an uptake assay to study tau internalization in primary cultures

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Abstract: Tauopathies, such as Alzheimer's disease (AD), are neurodegenerative disorders characterized by the deposition of hyperphosphorylated Tau in the form of aggregates such as neurofibrillary tangles (NFTs). Studies have shown that NFTs load correlates with neuronal death and the clinical symptomatology presented by patients, placing Tau as a key pathogenic player in AD. Recently, it has been proposed that proteopathic Tau seeds spread through the brain in a temporospatial pattern, indicative of trans-synaptic propagation. There is no complete understanding of the molecular mechanisms responsible for Tau seed uptake and the intracellular fate of these seeds leading to the induction of Tau aggregation. To unravel these molecular mechanisms, we have developed a cellular assay to measure Tau seed uptake and intracellular distribution making use of a high content/ high throughput imaging platform. In this work, we demonstrate how the labelling of Tau aggregates can be used both in fixed conditions and live-cell imaging. Automated analysis & quantification are applied to obtain unbiased measurements in defined cell-types and subcellular compartments. Our assay will allow to generate new insights in Tau seed uptake and intracellular fate.

Disclosures: **A.J. Carpinteiro Soares:** 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.; Janssen Pharmaceutica. **L. De Muynck:** A. Employment/Salary (full or part-time); Janssen Pharmaceutica. **W. Annaert:** None. **D. Moechars:** A. Employment/Salary (full or part-time); Janssen Pharmaceutica.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.01/R17

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

Title: Cocaine- and amphetamine-regulated transcript: A downstream regulator of nicotine's effect in rat model of Alzheimer's disease

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Abstract: Synaptic loss, neuronal death, and formation of neurofibrillary tangles and senile plaques are hallmarks of Alzheimer's disease (AD) resulting in memory loss and personality changes. Impairment of the cholinergic system contributes to AD and nicotine is identified as one of the few nootropic agents that ameliorate AD-like conditions. Nicotine is reported to reduce A β -induced toxicity, inhibit A β 42 aggregation and improve learning and memory in rodents and humans. Exogenous cocaine- and amphetamine-regulated transcript (CART) is known to improve memory in APP/PS1 mice. We wanted to find out if this nootropic activity of nicotine is promoted by CART in AD-like condition induced rats. Colchicine was administered via intracerebroventricular (icv) route to induce AD-like condition. While nicotine (intraperitoneal) or CART (icv) showed improvement in learning and memory in Morris water maze (MWM), CART-Antibody (icv) produced the opposite effects. This effect of nicotine in MWM was potentiated by the subeffective dose of CART, but antagonized by CART-Antibody. Colchicine-treated rat brains showed significant reduction in CART-immunoreactivity in accumbens shell, ventral bed nucleus of stria terminalis, central nucleus of amygdala, dentate gyrus, arcuate and paraventricular nucleus of hypothalamus, but not in CA1-3 regions. However, four days nicotine treatment in AD-induced animals significantly augmented CART-immunoreactivity in all the nuclei except CA1-3. In view of the recent evidences showing nicotinic receptors on CART neurons, we suggest that CART may be downstream to nicotinic system and play a role in improving the learning and memory in AD-like conditions.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

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Program #/Poster #: 049.02/R18

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

Support: NIH Grant AG027297

Kentucky Spinal Cord and Head Injury Research Trust 12-10A

The Hazel Embry Research Fund

NIH Grant AG056998

Title: Nuclear factor of activated T-cells 4 is up-regulated in astrocytes in aging canine brain model

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Abstract: Pathophysiological changes associated with Alzheimer's disease (AD) may be driven or exacerbated by the protein phosphatase calcineurin (CN). The most important implication of this hypothesis is that CN inhibitors could provide an attractive alternative or complimentary approach to anti-AD therapies currently under investigation in clinical trials. We are particularly interested in the role of astrocytes in this process, as our previous work implicated astrocyte activation in AD, and in particular, the CN-nuclear factor of activated T cells (NFAT) signaling pathway associated with astrocyte activation. Of the four CN-dependent NFAT isoforms, NFAT4 undergoes selective upregulation in activated astrocytes and provides a robust biomarker of injury and CN activation in astrocytes. Blocking this pathway, *in astrocytes*, ameliorates glutamate dyshomeostasis, neurodegeneration, synapse dysfunction, and cognitive loss in mouse models of AD. To demonstrate the broader implications of these findings, we propose to investigate the role of the CN-NFAT pathway in a more advanced model, the aging canine brain. Aged canines (beagle) show beta-amyloid accumulation in plaques and cognitive decline similar to early signs of AD in people. We have a bank of canine brain tissue from which we can draw samples for analyses. Focusing on NFAT4, we carried out Western analyses to determine the amount of NFAT4 expressed globally in cortex, and immunostaining and confocal microscopy to look at patterns of expression as well as overall levels in samples from aged (9.67-12.74 years old, n = 5) versus young brains (0.83-5.66 years old, n = 5). Our results demonstrate that NFAT4 expression is increased in aged canine brain, but exhibits robust labeling in activated astrocytes, regardless of age. Astrocytes surrounding and feeding into the vasculature were particularly well-labeled with NFAT4 antibody and the astrocyte marker, GFAP, while in other regions there

were astrocytes that expressed high levels of NFAT4 and lower levels of GFAP. Taken together, these data suggest there is heterogeneity in the astrocyte population, but NFAT4 is up-regulated in aged canine brain, consistent with our previous observations in rodent models. These results suggest that NFAT4 inhibition may be a target for intervention to prevent cognitive decline in the canine model of human aging and AD.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.03/S1

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

Support: NCF Grant LY14H310012

Title: Inhibition of phosphodiesterase-4 reverses A β -induced memory impairment by regulation of HPA axis related cAMP signaling

Authors: *Y. XU¹, H.-T. ZHANG², J. M. O'DONNELL¹, J. PAN³

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Abstract: Beta amyloid peptides (A β), the main component of the amyloid plaques in the brain of Alzheimer's disease (AD) patients, were found to be closely associated with cognitive and memory deficits. Phosphodiesterase 4 (PDE4) inhibitors increase the intracellular cAMP activities, which may ameliorate cognitive deficits associated with AD. However, it remains unclear whether PDE4-mediated reversal of cognitive impairment in AD mice is related to HPA axis and cAMP-dependent pathway. The present study investigated the effects of PDE4 inhibitor rolipram on A β 1-42-induced cognitive dysfunction and its underlying mechanisms. The step-down passive avoidance (PA) and Morris water-maze (MWM) tests were conducted 1 week (1 W), two months (2 M) and six months (6 M) after intracerebroventricular microinjection (i.c.v.) of A β 1-42. The results suggested that memory impairment emerged as early as 1 W, peaked at 2 M, and lasted until 6 M after injection. Chronic treatment with rolipram (0.1, 0.5, 1.0 mg/kg/d, i.p.) for 2 weeks (i.e. treatment started 1.5 months after A β 1-42 microinjection) dose-dependently improved memory performance in both MWM and PA tests. Moreover, rolipram reversed A β -induced increases in serum corticosterone (CORT), corticotropin-releasing factor (CRF) and glucocorticoid receptor (GR) levels and decreases in cAMP, brain derived neurotrophic factor (BDNF) and the ratio of pCREB to CREB expression. These effects of rolipram were

prevented by pre-treatment with PKA inhibitor H89. The findings indicated that the protective effects of rolipram against cognitive dysfunction produced by A β 1-42 might involve HPA axis and cAMP-CREB-BDNF signaling pathway.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.04/S2

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

Support: Alzheimer Society of Canada

Title: Repeated cold exposures protect old 3xTg-AD mice from cold-induced tau phosphorylation

Authors: *M. TOURNISSAC^{1,3,4}, P. BOURASSA^{1,3,4}, R. MARTINEZ³, E. PLANEL^{3,2}, S. HÉBERT^{3,2}, F. CALON^{1,3,4}

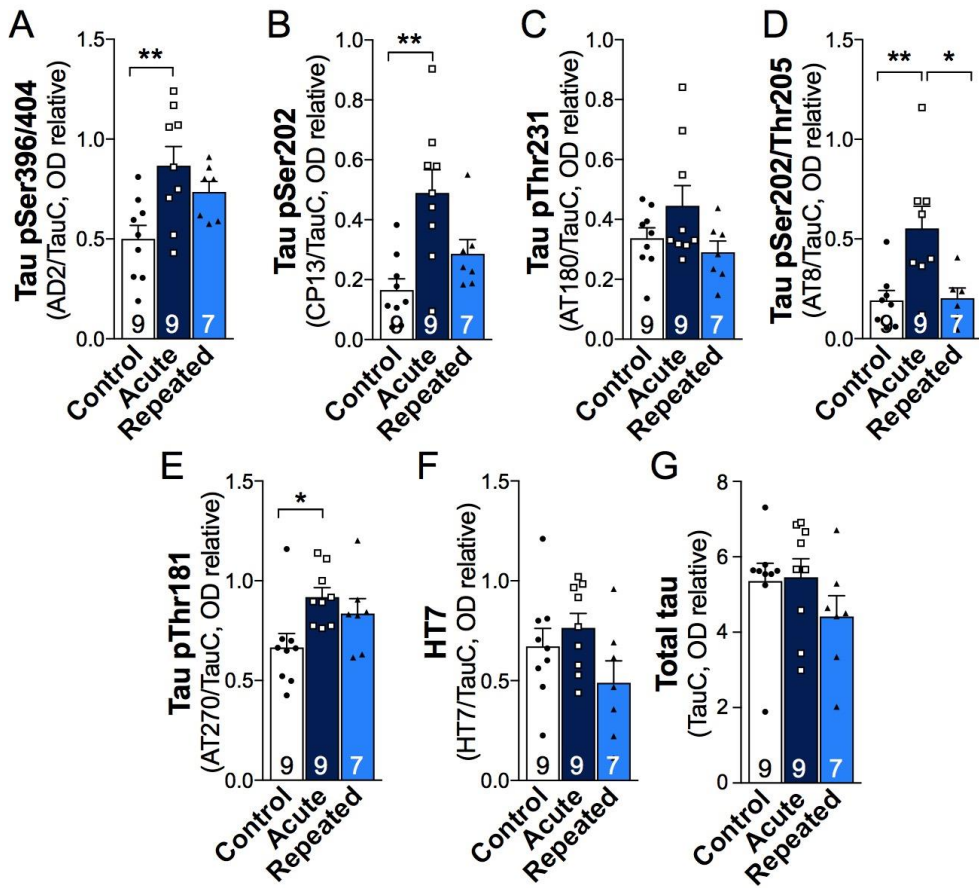
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⁴Inst. of Nutr. and Functional Foods, Laval Univ., Quebec, QC, Canada

Abstract: Old age is associated with a rise in the incidence of Alzheimer's disease (AD) but also with the occurrence of thermoregulatory deficits. Supporting a link between the two, we previously showed that old 3xTg-AD mice, besides tau and amyloid neuropathologies, also display metabolic and thermoregulatory defects. We notably observed that cold-induced tau hyperphosphorylation was aggravated in old 3xTg-AD mice. Brown adipose tissue (BAT) is the main thermogenic driver in mammals and its stimulation has repeatedly been shown to counteract metabolic deficits in diabetic mice and humans. Thus, we hypothesized that BAT stimulation could be of benefit in AD. To investigate the effect of BAT stimulation in an animal model of AD, we subjected 15-month-old 3xTg-AD mice to repeated short cold exposures (RSCE), consisting in 4-hour sessions of cold exposition (4°C), repeated 5 times a week during one month. At the end of the month, half of control and RSCE animals underwent an acute 24-hour exposure to cold. First, we confirmed that RSCE trained BAT thermogenesis, as established by a 2-fold rise in UCP1 expression and protection from a decrease in body temperature during the last acute cold exposure. Second, RSCE reversed glucose intolerance that develops in old 3xTg-AD mice, consistent with previously reported effects against metabolic impairments. Third, RSCE-trained old 3xTg-AD mice were completely resistant from the hyperphosphorylation of soluble tau in the hippocampus induced by an acute cold exposure (see

Figure). In contrast, insoluble phospho-tau as well as soluble and insoluble A β 40 and A β 42 peptides remained unchanged. Finally, RSCE induced a 66% increase in the levels of plasmatic fibroblast growth factor 21 (FGF-21), a BAT-secreted hormone, which correlated with hippocampal tau phosphorylation. In conclusion, BAT stimulation through repeated cold exposure reversed metabolic deficits and completely blocked cold-induced tau phosphorylation in the 3xTg-AD mouse model of AD neuropathology. These results suggest that improving thermogenesis could exert a therapeutic effect in AD.

Phosphorylation of soluble tau



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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.05/S3

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

Support: Departments of Industry and Education from the Basque Government KK-2017/14 Elkartek and IT975-16

Title: Learning and memory improvement mediated by CB₁ cannabinoid receptors in animal models of cholinergic dysfunction

Authors: M. MORENO-RODRÍGUEZ, J. MARTÍNEZ-GARDEAZABAL, A. LLORENTE-OVEJERO, L. LOMBARDERO, I. MANUEL, *R. RODRIGUEZ-PUERTAS
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Abstract: The selective vulnerability of the basal forebrain cholinergic system (BFCS) is responsible for most of the clinical alterations in learning and memory processes that are characteristic of the Alzheimer's disease (AD). The loss of cholinergic neurons and muscarinic receptors (MR) in the nucleus basalis of Meynert have been reported in AD. The endocannabinoid system is a neuromodulator of the BFCS, but there are controversial reports regarding the cannabinoid effects in learning and memory processes.

The animal models of cholinergic impairment mimic the main histopathological and behavioral effects observed in patients. The MR antagonism, e.g. using scopolamine (SCOP), is used as a model of amnesia in rodents. The intraparenchymal administration of 192-IgG-saporin (SAP) in the nucleus basalis magnocellularis eliminates cholinergic neurons leading to learning and memory deficits.

Then, the present study evaluates the modulation of spatial and working memory with the Barnes Maze following a subchronic treatment with a low dose (0.5 mg/kg) of WIN55,212-2 (WIN) in both the SCOP and SAP models of learning and memory deficit.

In the SCOP model, the administration of WIN protects learning and memory impairment during the probe trial, recorded as the time spent in the target quadrant (WIN + SCOP: 78 ± 13 sec vs VEH + SCOP: 45 ± 3 sec; $p < 0.001$). A similar effect of the treatment was observed in the SAP model (SAP: 50 ± 3 sec vs SAP + WIN: 82 ± 7 sec; $p < 0.001$). This effect was specifically mediated by CB₁ receptors, since it was blocked by the co-administration of the specific CB₁ antagonist, SR141716A (0.5 mg/kg) (SAP: 49 ± 3 sec vs SAP + WIN + SR: 48 ± 5 sec).

However, higher doses of WIN (3 mg/kg) induced negative effects in learning and memory in control (C) rats, but positive and comparable to the lower dose in the SAP model (C: 89 ± 3 sec, C + WIN-3 mg/kg: 48 ± 3 sec; SAP: 49 ± 3 ; SAP + WIN-3 mg/kg: 80 ± 12 sec; $p < 0.001$).

The CB₁ receptor activation by low doses of the cannabinoid agonist WIN are able to block the amnesic effects induced by SCOP and also the learning and memory impairment produced by the BFCS pathway degeneration. CB₁ agonists could contribute to improve the clinical symptoms of AD.

International application patent PCT/EP2018/054525.

Disclosures: **M. Moreno-Rodríguez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UPV/EHU. **J. Martínez-Gardeazabal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UPV/EHU. **A. LLorente-Ovejero:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UPV/EHU. **L. Lombardero:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UPV/EHU. **I. Manuel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UPV/EHU. **R. Rodríguez-Puertas:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UPV/EHU.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.06/S4

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

Support: MIS #201607071502 (Merck & Co.)

NIH-5P30-AG02838

Pilot grant: Univ. of Kentucky Dept. of Neuroscience

Title: The effects of pharmacological sleep enhancement using DORA-22 in the 5XFAD mouse model of Alzheimer's disease-related pathology

Authors: ***M. J. DUNCAN**¹, H. FARLOW¹, D. H. YUN¹, C. WANG¹, C. TIRUMALARAJU¹, J. A. HOWARD¹, M. N. SANDEN², K. J. MCQUERRY², B. F. O'HARA³, A. D. BACHSTETTER¹

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Abstract: Sleep disruption is a characteristic of Alzheimer's disease (AD) that impairs quality of life, challenges caregivers, and may contribute to memory deficits, increased neuroinflammation,

and exacerbated neuropathology. Whether sleep improvement will be beneficial in AD remains untested. Dual orexin receptor antagonists (DORAs) may be ideal candidates for sleep enhancement because unlike typical hypnotic drugs, DORAs increase both REM and NREM sleep and have a wide therapeutic index between sleep-inducing and memory-impairing effects. Therefore, we hypothesized that DORA-22 treatment would increase sleep in an AD-relevant mouse model and that the increased sleep would reduce amyloid-beta ($A\beta$) and neuroinflammation and would be associated with attenuation of memory deficits. To test this hypothesis, we used the 5XFAD mouse model of AD-related amyloidosis. By 6 months of age, the 5XFAD mice have profound $A\beta$ burden, neuroinflammation, and synaptic and cognitive dysfunction, as well as a concomitant sleep disruption, which make them an ideal model to test our hypothesis. Wild-type (WT, C57Bl/SJL) and 5XFAD mice (4 months old) of both sexes were treated daily, at the beginning of the light phase, with vehicle (20% vitamin-E TGPS) or DORA-22 (100 mg/kg) by oral gavage (N=10-12/genotype/sex/Rx) for 5 weeks. Body weight, recorded each week, was stable during the study. Mice were euthanized ~50 h after the last dose. Sleep was monitored with a piezoelectric system immediately before treatment and during the 5th week of treatment. The results confirmed that 5XFAD mice sleep less than WT mice ($p < 0.01$). In 5XFAD but not WT mice, DORA-22 treatment increased total sleep ($p < 0.02$) and sleep during the light phase ($p < 0.001$) and decreased sleep during the dark phase ($p < 0.05$), thus strengthening the daily sleep:wake rhythm. Mice were tested for short-term spatial memory via spontaneous Y-maze alternations, before the onset of treatment and during the 4th week of treatment. For unknown reasons, we were not able to detect a deficit in spontaneous alternations in the 5XFAD mice, and thus were not able to determine if DORA-22 attenuates cognitive deficits. DORA-22 treatment did not reduce $A\beta$ plaque density in the subiculum, neocortex, or hippocampus of 5XFAD mice, nor did it alter the expressions of many neuroinflammatory markers, which were markedly higher in 5XFAD than in WT mice. While DORA-22 increased sleep in 5XFAD mice, suggesting that treatment with a DORA such as Belsomra™ (Merck and Co.) may be feasible for improving sleep in AD patients, more work is warranted to determine optimal dose response, therapeutic window, and to test DORA-22 in additional AD-relevant animal models.

Disclosures: **M.J. Duncan:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; research contract for this study, Merck & Company. **C.** Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); drug (DORA-22), Merck & Company. **H. Farlow:** None. **D.H. Yun:** None. **C. Wang:** None. **C. Tirumalaraju:** None. **J.A. Howard:** None. **M.N. Sanden:** None. **K.J. McQuerry:** None. **B.F. O'Hara:** None. **A.D. Bachstetter:** None.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.07/S5

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

Support: REAP Grant 10261

Title: A non-pharmacological therapy improves spatial memory, waste clearance and neurotransmission in naturally aged rat model of Alzheimer's disease

Authors: H. TOBEY¹, D. BLEDSOE², T. LUCAS³, M. MYKINS¹, C. CAMPBELL¹, S. S. BERR⁵, T. SASSER⁶, C. MOLINOS⁷, R. HELM⁸, L. SHAN¹, P. BROLINSON¹, *B. G. KLEIN⁴, B. M. COSTA⁹

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Abstract: In the aging brain, reduction in the pulsation of cerebral vasculature and reduced fluid circulation cause impairment in fluid exchange between different compartments that pave a foundation for neuroinflammation that results in Alzheimer's disease (AD). The role of CNS lymphatic vessels in clearance of brain derived metabolic waste products opens an unprecedented capability to increase the clearance of macromolecules such as amyloid beta (A β) proteins. However, currently, there is no physiological or pharmacological mechanism available to increase fluid circulation in the aging brain. In the present study, we demonstrate a significant improvement in spatial memory after seven days of cranial osteopathic manipulation (COM) therapy, in a naturally aged rat model of AD. Immunoassay analysis and live animal PET imaging reveal that COM treatment reduces A β levels, activates astrocytes and improves excitatory neurotransmission in aged rat brain. These findings, for the first time, demonstrate a mechanism of COM treatment that has been clinically practiced for decades that will help clinicians promote COM as an evidence based adjunct treatment strategy for AD.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.08/S6

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

Support: NIH Grant R01 NS094595

Title: Systemic AAV-mediated gene delivery of a mutant form of EPO restores cognitive abilities and reduces neuropathology in 5xFAD mice

Authors: *D. F. DELOTTERIE¹, L. L. SOMERVILLE¹, J. T. KILLMAR¹, Y. XUE¹, T. S. REX³, M. P. MCDONALD^{1,2}

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Abstract: Primarily secreted in the kidney and liver in mammals, erythropoietin (EPO) is a glycoprotein cytokine originally recognized for its contribution to the regulation of red blood cell production. Compelling evidence suggests additional biological functions in the central nervous system, where EPO has been found to promote neuroprotection and stimulate hippocampal neurogenesis. In the present study, we sought to assess whether such beneficial effects would be observed after recombinant adeno-associated viral (rAAV) vector-mediated treatment with EPO-R76E - a modified form of EPO devoid of major erythropoietic activity - in an animal model of Alzheimer's disease. Following initial training in a Delayed Non-Matching To Position (DNMTP) touchscreen task, male and female 5xFAD animals and their non-transgenic littermates were given a single 10- μ L intramuscular injection of rAAV.EPO-R76E or enhanced green fluorescent protein (rAAV.eGFP) at 6 or 12 months of age; after a 6-week period ensuring effective viral transduction, mice were re-trained to performance levels in operant chambers. Three months after injection, a comprehensive battery of anxiety, sensorimotor, and cognitive tasks was conducted. At 10 or 16 months of age, blood, brain and spinal cord tissues were collected. Soluble and insoluble amyloid beta (A β) levels were quantified while inflammatory and synaptic biomarkers were examined by immunohistochemistry. Regardless of the age at which treatment was provided, EPO-R76E was associated with increased neuroprotection and lower neuroinflammation in 5xFAD mice. Behavioral effects varied across age: in younger transgenics, EPO-R76E preserved memory; in older transgenics, EPO-R76E mostly ameliorated balance and coordination. Hematocrit levels were comparable among all experimental groups. Viral-mediated EPO-R76E gene therapy therefore represents a promising therapeutic agent for motor and cognitive symptoms of Alzheimer's disease.

Disclosures: D.F. Delotterie: None. L.L. Somerville: None. J.T. Killmar: None. Y. Xue: None. T.S. Rex: None. M.P. McDonald: None.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.09/S7

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

Support: Council of Scientific and Industrial Research, India

Title: Neuroprotective effect of phycocyanin in experimental paradigms of STZ induced Alzheimer's disease

Authors: *M. AGRAWAL¹, Y. PERUMAL¹, S. BANSAL², S. ARORA¹, R. DHARAVATH¹, K. CHOPRA¹

¹Dept. of Pharmacol., Panjab Univ., Chandigarh, India; ²Dept. of Pharmacol., Postgraduate Inst. of Med. Educ. and Res., Chandigarh, India

Abstract: Introduction: Alzheimer's is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function through loss of cortical neurons, especially pyramidal cells, that mediate higher cognitive functions. Worldwide, nearly 44 million people have Alzheimer's or a related dementia. Phycocyanin has been demonstrated in number of pharmacological activities including anti-cancer, anti-oxidant and anti-inflammatory activities. In lieu of these merits we decided to explore it as a neuroprotective agent. **Methodology:** Intracerebroventricular injection of Streptozotocin 3mg/kg was given. Rats were anesthetized with Ketamine-Xylazine. The scalp was shaved, cleaned and cut to expose the skull. The head was positioned in a stereotaxic frame, and a midline sagittal incision was made in the scalp. Burr holes were drilled in the skull on both sides over the lateral ventricles by using the following coordinates: 0.8 mm posterior to bregma, 1.5 mm lateral to sagittal suture and 3.6 mm beneath the surface of the brain. Total volume of ICV injection was 6 µl of STZ or ACSF bilaterally (3 µl/burr hole). The skin was sutured after injection followed by daily application of antiseptic powder (Neosporin). Postoperatively, the rats were fed with oral glucose and normal pellet diet for 4 days, followed by normal pellet diet alone. Cognitive performance, Memory test, locomotive activity etc were assessed utilising various behaviour parameters (Morris Water Maze, Open Field Test, Novel Object Recognition. On last day (28th) the animals were sacrificed and desired parts of rat brain (Cortex, Hippocampus) were isolated for further biochemical estimations (Lipid peroxidation, Nitrite estimation, Superoxide dismutase activity, reduced glutathione) and molecular estimations.

Results: Phycocyanin (50 and 100 mg/kg) significantly confined all the behavioural alterations,

and oxidative damage along with down regulating pro inflammatory cytokines in dose dependant manner. Our finding suggests that phycocyanin is capable of restoring ACh levels in ICV-STZ injected rats, as well as normalizing AChE activity. Study also reveal that neuroprotective effect of the drug is mediated through PI3K/AKT/mTOR activation, suggesting that phycocyanin may be explored further as a potent candidate for Alzheimer's disease therapy.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.10/S8

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

Title: A potential tri-therapy for Alzheimer's disease

Authors: ***A. Y. BRUREAU**, N. CHOLET, J. FOUCQUIER, R. HAJJ, D. COHEN
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Abstract: Cognitive symptoms in Alzheimer's disease (AD) are currently managed by moderately acting standards of care which efficacy decreases fast over time and use is often accompanied by side effects. We previously showed that a combination of acamprosate and baclofen (PXT864) synergistically prevented cognitive impairments in AD mice. In this study, we investigated whether PXT864 could i) protect cognitive functions by synergizing with sub-therapeutic doses of donepezil (DNPz) to limit the occurrence of adverse events, or ii) rescue the efficacy of DNPz that is lost over time under therapeutic doses. We used the A β ₂₅₋₃₅ intracerebroventricular (ICV) injection mouse model that mimics AD features. We tested first PXT864 in combination with sub-therapeutic doses of DNPz, both administered to mice before A β ₂₅₋₃₅ injection (prevention protocol). Second, we modeled the loss of activity of DNPz treatment over time when initiated after A β ₂₅₋₃₅ ICV injection (interventional protocol). Third, once DNPz effect was lost, we added PXT864 to DNPz and assessed the value of such tri-therapy. Efficacy was assessed by Y-maze and step-through passive avoidance behavioral cognitive tests. When mice were treated before A β ₂₅₋₃₅ ICV injection, we found that combining PXT864 with sub-therapeutic doses of DNPz yielded synergistic protection against A β -induced cognitive deficits. Then we showed in AD mice comparable efficacy kinetics of DNPz to the one observed in AD patients, which is a cognitive decline over time at a later stage of the disease when treatment was started after A β ₂₅₋₃₅ ICV injection. Interestingly, adding PXT864 at that stage fully restored lost cognition in these animals that became all irresponsive to DNPz. Assessment of hallmark molecular markers of AD showed also the same improvement in favor

of the triple combination. These data highlight the importance of combinational strategies and suggest that PXT864 could be used either as a first line treatment or as a second line treatment with a safe sub-therapeutic or even a full therapeutic dose of DNPz in Alzheimer's patients.

Disclosures: **A.Y. Brureau:** A. Employment/Salary (full or part-time);; Pharnext. **N. Cholet:** A. Employment/Salary (full or part-time);; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext. **J. Fouquier:** A. Employment/Salary (full or part-time);; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext. **R. Hajj:** A. Employment/Salary (full or part-time);; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext. **D. Cohen:** A. Employment/Salary (full or part-time);; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.11/S9

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

Support: BMBF grant FKZ 031A575A

Title: Intravenous delivery of bone marrow mesenchymal stem cells in a transgenic mouse model of Alzheimer's disease

Authors: ***L. DANIELYAN**¹, **S. STEINBRUECKER**¹, **A. LOURHMATI**¹, **M. BUADZE**¹, **K. ARNOLD**², **C. FABIAN**², **A. STOLZING**², **H. NGUYEN**³, **M. SCHWAB**¹

¹Univ. Hosp. of Tuebingen, Tuebingen, Germany; ²Fraunhofer Inst. for Cell Therapy and Immunol. (IZI), Leipzig, Germany; ³nstitute of Med. Genet. and Applied Genomics, Univ. of Tuebingen, Tuebingen, Germany

Abstract: *Objectives* Bone marrow mesenchymal stem cells (MSC) have been proven experimentally to be efficacious cell candidates for a variety of brain disorders including Alzheimer's disease (AD). Our previous study demonstrated that therapeutic efficacy of intranasally delivered MSC is superior to that of intracerebral MSC transplantation. Here we sought to evaluate the effects of intravenous (i.v.) MSC administration on the spatial memory, microglial activation and amyloid beta degrading enzyme neprilysin in a transgenic mouse model of AD.

Methods Mouse eGFP-MSCs vs. vehicle were administered intravenously to 6-month old 3xTg-AD mice. Memory deficit was monitored one week prior and 3 weeks after MSCs transplantation by forced choice alternation T-maze. Brain homogenates were analyzed for the expression of choline acetyltransferase (ChAT), synaptophysin, CD-68, CD206, Iba-1 and neprilysin. Results Spatial memory was improved by MSCs in the last week of testing. Western Blot analyses revealed an increase in ChAT and neprilysin in MSC-treated group, while synaptophysin, CD68, CD206 and Iba-1 remained unchanged. In contrast to our previous data on intranasal delivery of MSC showing a successful and efficacious delivery of MSC to the brain (especially to the hippocampus and cortex), eGFP-MSC could not be detected in the brains of 3xTg-AD after intravenous administration.

Conclusions In a view of the invasiveness of surgical transplantation and consequently low survival of transplanted cells due to the strong inflammatory response to intracerebral injection, the successful establishment of non-invasive delivery methods allowing for repeated cell administration and avoiding inflammation provides an improved strategy for cell-based therapy of central nervous system disorders. Intravenous and intranasal administration of MSCs appear to have in common their influence on the expression of ChAT, neprilysin and markers of microglial activation and phagocytosis. However, the effect of intranasal MSC on the spatial memory and synaptogenesis is superior to that of MSC after i.v. administration. In addition the delivery of cells to the brain by intranasal administration is far more reliable and efficacious than after i.v.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.12/S10

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

Support: Canadian Institutes of Health Research (MOP-126001)
Canadian Vascular Network-Hypertension Canada Scholar Award
FRQS doctoral studentship

Title: Angiotensin II type 2 receptors exert selective cerebrovascular but no cognitive benefits in an Alzheimer's disease mouse model

Authors: *J. ROYEA, M. LACALLE-AURIOLES, L. J. TRIGIANI, A. FERMIGIER, E. HAMEL

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Abstract: Background: The risk of developing Alzheimer's disease (AD) increases with each vascular risk factor, with hypertension being the primary cardiovascular risk. Studies show that antihypertensive medications targeting the renin angiotensin system lower the incidence and progression to AD¹. Particularly, the angiotensin II (AngII) type 1 receptor (AT1R) antagonist losartan has been shown to restore cerebrovascular and cognitive deficits in AD mouse models². Angiotensin IV receptors (AT4Rs) have been implicated in losartan's benefits³, but whether AT4Rs act alone or with AngII type 2 receptors (AT2Rs) is unclear. We investigated whether AT2Rs mediate benefits of chronic losartan treatment and whether chronic administration of an AT2R agonist could mimic losartan's benefits in AD transgenic mice overexpressing the Swedish and Indiana mutations of the human amyloid precursor protein (APP mice, line 20).

Methods/Results: Wild-type and APP mice (2-3 months old) received losartan (10 mg/kg/day, drinking water, 7 months). Losartan treated mice received intracerebroventricular (icv) administration of CSF (control) or AT2R antagonist PD123319 (1.6 nmol/day), whereas some untreated mice were administered the AT2R agonist Compound 21 (C21, 1 nmol/day, icv) via osmotic minipumps. PD123319 failed to counter losartan's cognitive benefits measured in the Morris water maze (MWM) and novel object recognition (NOR) tests. C21 treatment had no benefit on any memory parameter. PD123319 countered losartan's ability to rescue sensory-evoked neurovascular coupling while C21 normalized this response in APP mice. Losartan's benefits on nitric oxide (NO) bioavailability was reduced by PD123319 administration, while C21 improved NO bioavailability. Neither PD123319 or C21 treatment altered endothelial- or smooth muscle dilatory function.

Conclusions: AT2Rs contribute to neurovascular coupling and NO bioavailability benefits following chronic AT1R blockade in APP mice. Since AT2Rs failed to counter and AT2Rs agonism failed to mimic losartan's cognitive benefits, our results suggest that AT2Rs may not be a fully effective therapeutic approach for AD. We conclude that the decreased incidence of AD in hypertensive patients treated by ARBs⁴ may be related to AT4R rather than AT2R activation.

References:

1. Khachaturian *et al*, Arch Neurol, 2006, 686-692 ; 2. Ongali B *et al*, Neurobiol Dis, 2014, 126-136; 3. Royea J *et al*, J Neuroscience, 2017, 5562-5573; 4. Wolozin B *et al*, Alzheimers Dement, 2008, 182-185.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.13/S11

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

Support: NIA/NIH Grant 1R25AGO47843-01

Title: The impact of metformin treatment and voluntary running on alzheimer's disease-related neuropathology in a transgenic mouse model

Authors: *A. JALDI¹, O. BELLO², T. AJISEBUTU², T. FALEGAN², D. LEE¹, V. MULGRAVE³, T. SMITH², J. ALLARD¹

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Abstract: Several studies have shown a link between AD and Type-2 Diabetes Mellitus (T2DM). It has also been demonstrated that AD brains, regardless of the presence of T2DM, exhibit insulin resistance or insulin insufficiency. The overall goal of this study is to understand the impact of the insulin-sensitizing drug metformin and voluntary exercise on amyloid-beta plaque deposition, levels of neurotrophic factors and pro-inflammatory cytokines using an adult, female APP/PS1 mouse model. Animals were categorized into exercise, sedentary, metformin treated and untreated groups. Voluntary running-wheel activity was monitored and metformin was given at a dose of 70 mg/kg body weight for one year. Preliminary results reveal a significant increase in voluntary running activity of mice treated with metformin. The combination of metformin and voluntary exercise did not affect amyloid-beta plaque load in the hippocampus. Data also reveals differential effects of metformin treatment on brain and skeletal muscle BDNF mRNA levels. These results provide new information on the effects of metformin in combination with exercise on AD-like pathology.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

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Program #/Poster #: 049.14/S12

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

Support: UCI MIND T32 AG000096-33

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ICTS UL1 TR001414

DOE GAANN P200A120165

Title: The anti-epileptic drug Levetiracetam partially restores impaired hippocampal long-term potentiation in mice lacking synaptic zinc

Authors: *M. MAHAVONGTRAKUL, C. COX, E. KRAMAR, J. NOCHE, R. CAMPBELL, A. TRAN, C. CHINN, M. WOOD, J. BUSCIGLIO

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Abstract: While it has been known for a while that patients with Alzheimer's Disease (AD) have increased risk of unprovoked seizures, only recently has hyperexcitability become a major focus of AD research. Increased hippocampal activity in patients with mild cognitive impairment (MCI) was initially thought to be a beneficial compensatory mechanism; however, recent research has shown that patients with MCI who are treated with antiepileptic drugs have improved cognition. Synaptic zinc, co-released with amyloid- β ($A\beta$) during neurotransmission, is implicated in both oligomer formation and modulation of excitatory neurotransmission. Synaptic zinc is packaged into synaptic vesicles by ZnT3; thus, *ZnT3*^{-/-} mice lack synaptically-released zinc. These mice exhibit increased susceptibility to seizures and synaptic dysfunction, consistent with the finding that synaptic zinc is sequestered by $A\beta$ oligomers. In fact, *ZnT3*^{-/-} mice exhibit age-dependent increases in markers of seizure activity, synaptic loss, and neurodegeneration. In addition, we have recently shown that chronic, but not acute, treatment with the antiepileptic drug Levetiracetam (LEV) prevents cognitive decline in these mice. Chronic LEV also restores neurogenesis specifically in female *ZnT3*^{-/-} mice, indicating sex-specific mechanisms of action. Previous research in our lab has also indicated sex-specific gene alterations in *ZnT3*^{-/-} mice following treatment with chronic LEV including genes involved in neuronal excitability, epigenetics, and synaptic plasticity. To further understand the effect of LEV at both the systems and cellular level, we examined: 1) electroencephalogram (EEG) activity, and 2) long-term potentiation (LTP), in male and female *ZnT3*^{-/-} mice chronically treated with LEV. EEG measurements suggested that although *ZnT3*^{-/-} mice of both sexes exhibited significantly higher levels of spiking, chronic LEV had no effect on EEG spiking nor in overall EEG power

characteristics. *ZnT3*^{-/-} hippocampal slices subjected to theta burst stimulation consistently showed deficits in LTP levels in both sexes. Chronic LEV partially restored LTP in female *ZnT3*^{-/-} mice, but completely rescued the impairment on LTP in male *ZnT3*^{-/-} mice. These results indicate that *ZnT3*^{-/-} mice exhibit mild alterations in spiking activity and LTP deficits similar to the ones observed in APP/AD mouse models, further implicating synaptic zinc in the pathophysiology of AD. At a cellular level, chronic LEV restores LTP in *ZnT3*^{-/-} mice, providing a potential rationale for the use of chronic LEV to prevent or ameliorate cognitive impairment in AD.

Disclosures: M. Mahavongtrakul: None. C. Cox: None. E. Kramar: None. J. Noche: None. R. Campbell: None. A. Tran: None. C. Chinn: None. M. Wood: None. J. Busciglio: None.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.15/S13

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

Support: Alzheimer Society of Canada Doctoral Scholarship to LZ
CIHR Operating Grant 126137 to PJS
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Title: Methylene blue reverses caspase-6-mediated cognitive deficits in mice

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Abstract: Caspase-6 (Casp6) is abnormally activated in Alzheimer disease (AD) neuropil threads, neuritic plaques, and neurofibrillary tangles. Casp6 activity in non-cognitively impaired (NCI) individuals is restricted to the entorhinal cortex and hippocampal CA1 regions, the first areas presenting neurofibrillary tangles in AD. High Casp6 levels correlate with lower episodic and semantic memory in aged NCI individuals. In vitro, Casp6 activity induces axonal degeneration by cleaving cytoskeleton and cytoskeletal-associated proteins. Transgenic expression of active human Casp6 (hCasp6) in mouse hippocampal CA1 is sufficient to cause

age-dependent cognitive deficits. The goal of this study is to investigate whether Casp6-induced cognitive impairments are reversible. Methylene blue (MB) was used as the Casp6 inhibitor because it is safe, blood-brain barrier permeable, and in clinical trials as a Tau aggregation inhibitor. We treated 18-month hCasp6 mice 20 mg/kg/d MB orally for one month. Episodic and spatial memory, and locomotor activity were measured with novel object recognition, Barnes maze, and open field, respectively. Theta-burst long-term potentiation (LTP) at the hippocampal Schaffer collateral-CA1 pathway was assessed in acute brain slices. Cleaved α -tubulin by Casp6 (Tub Δ Casp6), microglia, and astrocyte were analyzed by immunohistochemistry with a neoepitope antiserum, Iba1, and GFAP, respectively. MB reversed Casp6-induced episodic and spatial memory impairments. Locomotor problems and thigmotaxis were excluded as possibilities for hCasp6 mice poor performance in cognitive tasks. MB rescued Casp6-induced Schaffer collateral-CA1 synaptic dysfunction since LTP was successfully induced in MB-treated hCasp6 mice. Human Casp6 immunoreactivity was limited to CA1 regions; however, Tub Δ Casp6 staining, reflecting Casp6 activity, was located in CA1, hippocampal commissure, fornix-fimbria, corpus callosum, and internal capsule. Active microglia and astrocytes increased in the hippocampal commissure, fornix-fimbria, the corpus callosum, and internal capsule. The levels of Tub Δ Casp6, active microglia, and astrocytes did not change in hippocampal CA1, but significantly decreased in all regions composed of axon bundles in MB-treated hCasp6 mice. These results indicate that MB reversed Casp6-induced cognitive deficits, possibly by rescuing hippocampal axon degeneration. Our results suggest that, in addition to preventing Tau disaggregation, MB could benefit AD by also preventing Casp6-dependent cognitive decline.

Disclosures: L. Zhou: None. P.J. Sjostrom: None. A.C. LeBlanc: None.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.16/S14

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

Support: Bourse de mobilité Idex Bordeaux

LIA OptiNutriBrain

CIHR (MOP 125930)

FRQS (#26936)

Title: Tetrahydrobiopterin as a potential treatment for Alzheimer's disease: A study in 3xTg-AD mice

Authors: *F. CALON¹, M. TOURNISSAC^{1,2}, A. LO³, C. TREMBLAY¹, P. BOURASSA¹, V. EMOND¹, F. MOUSSA³, S. VANCASSEL^{4,2}, H. FANET^{1,2,4,5}

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Abstract: Alzheimer's disease (AD) is a multifactorial disease, thus multi-target treatments are needed. Tetrahydrobiopterin (BH4) has been shown to be decreased in elderly and in AD patients. BH4 is an enzymatic cofactor required for the synthesis of serotonin (5-HT), dopamine (DA) and nitric oxide. It also exerts strong antioxidant and anti-inflammatory effects. Thus, BH4 administration could ameliorate monoaminergic neurotransmission but also other key physiological processes such as vascularization, metabolism, inflammatory and oxidative status. Surprisingly, despite its crucial role in the CNS, the potential of BH4 as a treatment in AD has never been investigated. Thus, we hypothesized that BH4 administration can ameliorate both cognitive symptoms and AD neuropathology. Non-transgenic (NonTg) and 3xTg-AD mice, which display age-related behavior impairment, tau and A β neuropathologies, were subject to a high-fat diet (35% fat - HFD) or control diet (5% fat - CD) from 6 to 13 months in order to exacerbate inflammatory and metabolic disturbances. Then, mice were injected intraperitoneally with BH4 (15mg/kg) or control solution during ten days. To verify whether BH4 is a suitable therapeutic for the CNS, we first demonstrated that peripheral administration of BH4 (50mg/kg) was sufficient to double BH4 brain content within 3h. Using in-situ brain perfusion, we found that the brain uptake clearance (Cl_{up}) of BH4 was approximately 0.08 μ l/g/sec, consistent with a modest transfer across the BBB. For the first time, we report that ten days of chronic administration of BH4 induced a total rescue of memory impairment in 13-month-old 3xTg-AD mice as determined with the novel object recognition test. Interestingly, this improvement was observed even over a HFD background. Moreover, glucose intolerance induced by HFD in 3xTg-AD mice was completely reversed by BH4 treatment while no difference on diet consumption, mice weight and voluntary locomotion in open-field were observed. BH4 treatment had no effect on total or phosphorylated tau assessed in soluble and insoluble fractions extracted from the hippocampus. As BH4 is involved in monoamine synthesis, we also measured striatal DA and 5-HT content without detecting any significant changes. Amyloid pathology and pro-inflammatory cytokines measurements are currently ongoing. Overall, our data show that BH4 supplementation leads to a rescue in object recognition memory and metabolic impairments in the 3xTg-AD mouse model, without altering tau neuropathology.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.17/S15

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

Support: NIH Grant AG045031

NIH Grant AG056901

Title: Perinatal choline supplementation ameliorates Alzheimer's disease (AD) neuropathology and increases brain expression of BMP9 - a trophic factor for cholinergic neurons - while BMP9 deficiency increases vulnerability to AD-related pathology and cognitive deficits in rodent models

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Abstract: This study was designed to test the hypothesis that the long-term induction of expression of the growth and differentiating factor, bone morphogenetic protein 9 (BMP9 also known as GDF2), mediates the cognitive enhancing- and anti-amyloidogenic actions of perinatal choline supplementation. Choline is an essential nutrient required for normal growth and development, however, multiple studies have shown that most Americans consume much less than the adequate intake (AI) value for this nutrient. We previously showed that maternal choline intake during pregnancy governed cognitive development and aging of the offspring in a rat model, specifically that perinatal choline supplementation prevented the memory decline normally observed in aged rats. We analyzed mRNA purified from rat hippocampus using RT-PCR and now report that perinatal choline supplementation generated a trophic brain microenvironment by increasing the expression of several growth factors, including *Bmp9*, as compared to controls. BMP9 is a differentiating and maintenance factor of the cholinergic phenotype of the basal forebrain cholinergic neurons (BFCN) - a population of cells that participate in the processes of learning and memory. A decline in BFCN function and diminished cholinergic marker expression is apparent in aged humans and animals, in patients with AD and in animal models of AD. We showed that administration of BMP9 ameliorates the amyloidosis and reverses the cholinergic defect in the transgenic APP.PS1 mice that serve as a model of AD. In this study, we crossed WT-*Bmp9*^{+/-} females with hemizygous APP.PS1 males that were either *Bmp9*^{+/+} or *Bmp9*^{-/-}. Both male and female offspring were behaviorally tested at 8 and 12 months of age and results were analyzed in a blinded fashion. We found that APP.PS1 mice

that lack BMP9 due to the targeted mutation of its gene (*Bmp9*^{-/-} mice) were characterized by increased vulnerability to the AD-like pathology as evidenced by greater memory defects (Barnes maze) and decreased expression of cholinergic markers in the hippocampus and septum as compared to APP.PS1 mice that express BMP9 (*Bmp9*^{+/+}). These data suggest that dietary supplementation with choline during early life may constitute a preventive strategy for AD and, together, they are consistent with the hypothesis the mechanism of action of choline may include the induction of BMP9 expression in brain.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.18/S16

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

Support: NIH Grant R01 AG050431

Zenith Fellows Award (ZEN-17-438829) from Alzheimer's Association

Merit award (I01BX002174) from Veteran Affairs

Title: Aspirin modulates hippocampal plasticity and improves memory via transcriptional activation of PPAR α in the mouse model of Alzheimer's disease

Authors: *D. PATEL¹, A. ROY^{1,2}, K. PAHAN^{1,2}

¹Dept. of Neurolog. Sci., Rush Univ. Med. Ctr., Chicago, IL; ²Div. of Res. and Develop., Jesse Brown Veterans Affairs Med. Ctr., Chicago, IL

Abstract: Memory loss is the earliest and most prominent symptom associated with progressive dementia in Alzheimer's disease (AD). To date, FDA has approved very few drugs for the treatment of AD-related dementia. These drugs only provide limited symptomatic relief but can cause unpleasant side effects like loss of appetite, nausea, vomiting and diarrhea. Therefore, finding new safer drugs that can slow down or prevent memory deficits in AD patients is presently an active area of extensive research. Recently, we found that aspirin, one of the most widely used medicines in the world, is capable of stimulating hippocampal plasticity and protecting memory. We investigated the underlying mechanism involved in aspirin mediated modulation of hippocampal plasticity by employing array of proteomic analyses coupled with cheminformatics, thermal shift assays, TR-FRET and GC MS. Our detailed proteomic analyses revealed that aspirin, serves as a peroxisome proliferator activated receptor alpha (PPAR α)

ligand through direct binding at the Tyr314 residue of the PPAR α ligand-binding domain (LBD). Next, we validated our *in-silico* analyses through different cell-based assays that include chromatin immunoprecipitation, PPRE luciferase assays and calcium influx assays. We observed that upon binding to PPAR α LBD, aspirin induces the activation of PPAR α to upregulate the transcription of *Creb* gene and associated hippocampal plasticity. Furthermore, our hippocampus-dependent behavioral analyses, immunoassays of synaptic proteins, AMPA and NMDA induced calcium influx assays in hippocampal slices, and quantification of dendritic spines demonstrated that low-dose aspirin treatment improved hippocampal plasticity and memory in FAD5X, but not in FAD5X/Ppara-null mice. Taken together, these findings highlight that aspirin, a widely used analgesic, binds to the ligand-binding domain of PPAR α and upregulates hippocampal plasticity through transcriptional activation of PPAR α . We also demonstrate that after oral administration, aspirin improves hippocampal functions and protects memory in an animal model of AD via PPAR α . Therefore, low-dose aspirin may find its therapeutic use in AD as well as other dementias.

Disclosures: D. Patel: None. A. Roy: None. K. Pahan: None.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.19/S17

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

Support: NIH R01 AG 040092 (CAL)
an unrestricted gift from Probiodrug AG (CAL)

Title: Therapeutic efficacy of a novel CDC-mutant anti-pyroGlu3 Abeta IgG2a antibody (07/2a-k) without increasing microhemorrhages in aged APP/PS1dE9 mice

Authors: *K. MAKIOKA^{1,2}, N. MAKIOKA^{1,2}, Q. SHI^{1,2}, B. LIU^{1,2}, G. G. LIU^{1,2}, B. J. CALDARONE^{3,4}, M. KLEINSCHMIDT^{5,6}, J.-U. RAHFELD^{5,6}, I. LUES⁵, S. SCHILLING^{5,6}, C. A. LEMERE¹

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Abstract: Pyroglutamate-3 amyloid- β (pGlu-3 A β) is an N-terminally truncated and modified A β species typically found in plaques and water-soluble extracts from Alzheimer's disease (AD)

brain. The N-terminal modification by pGlu renders A β resistant to degradation by aminopeptidases and increases its aggregation propensity to form neurotoxic oligomers and deposits. Thus, pGlu-3 A β plays an important role in AD pathology, and immunotherapy targeting pGlu-3 A β is under investigation. To date, many clinical trials of A β immunotherapy have not met their cognitive or functional endpoints, possibly due to the inclusion of non-AD patients, saturation of antibody binding in blood, and low penetration of antibodies into the brain at doses required to avoid vascular edema or hemorrhages. Thus, there is a need to increase delivery of antibodies into brain while avoiding potential vascular inflammatory side effects. Previously, we reported that chronic treatment with an anti-pGlu-3 A β IgG2a mAb (07/2a) in 12 mo-old APP/PS1 Δ E9 Tg mice demonstrated significant cognitive improvement and plaque reduction 4 mo later (Crehan, SfN 2015). To avoid vascular inflammatory side effects, a mutation in the CDC region of the 07/2a mAb was introduced (07/2a-k), rendering it unable to activate the complement system. Here, plaque-rich 13 mo-old male APP/PS1 Δ E9 mice received 16 weekly i.p. injections of 07/2a (300 μ g), 07/2a-k (300 μ g), an IgG2a isotype control mAb (300 μ g) or PBS, and then underwent Open Field (OF) and Water-T Maze (WTM) behavioral testing. All mice were euthanized at 17 mo, and brains were collected and processed for biochemical and immunohistochemical analyses. No treatment effects were seen on locomotor activity or anxiety in the OF test. However, 07/2a-k treated Tg mice showed a strong trend ($p=0.06$) for an increased percent of mice that reached criterion on Day 5 of the WTM reversal test compared to IgG2a isotype controls, indicating improved memory. Hippocampal pGlu-3 A β immunoreactivity was significantly reduced in 07/2a- and 07/2a-k-treated Tg mice compared to IgG2a isotype- and PBS-treated controls. Importantly, anti-pGlu-3 A β immunotherapy did not increase microhemorrhages, detected by hemosiderin, compared to controls. In summary, these initial data suggest that the CDC mutant pGlu-3 IgG2a mAb has the potential to lower plaque burden and spare cognitive decline without vascular side effects in aged APP/PS1 Δ E9 mice. Further pathological and biochemical analyses are underway.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.20/S18

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

Support: FRSQ 34575
CIHR ERT144213

Title: Development of oral plasmalogen precursors for the treatment of Alzheimer's disease: Clinical proof-of-concept in the pediatric orphan disease rhizomelic chondrodysplasia punctata

Authors: *T. M. SMITH¹, W. FALLATAH², D. JAYASINGHE¹, S. A. RITCHIE¹, N. BRAVERMAN²

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Abstract: Alzheimer's disease (AD) is associated with reduced levels of ethanolamine plasmalogens (PlsEtn) in the serum and brain, with deficiencies preceding the onset of symptoms by 7+ years. The characteristic vinyl-ether bond of PlsEtn impacts membrane structure, vesicular fusion, and lipid raft assembly. Compromised PlsEtn levels reduce the propensity of membranes to undergo vesicular fusion, impairing neurotransmitter release and uptake. Membrane PlsEtn composition also affects APP processing and favors non-amylogenic processing. Plasmalogen deficiency is thus suggested to contribute to the onset and progression of AD. Our hypothesis is that pharmacological replacement of PlsEtn will improve symptoms and possibly prevent or delay the onset of AD. With this goal, we developed a series of synthetic plasmalogen precursor intermediates (PPIs) as a novel therapeutic strategy for the treatment of AD. To begin to study the pharmacokinetic properties of PPIs, we used a mouse model for the rare pediatric disease Rhizomelic chondrodysplasia punctata (RCDP), caused by genetic mutations that prevent PlsEtn biosynthesis. The Pex7^{Hypo/Null} animal model mimics deficiency of PEX7, the most common cause of RCDP. This model shows reduced plasmalogen levels and increased activity level in the open field environment. In the data presented herein, we report the results of the Pex7^{Hypo/Null} mice treated orally at 50 mg/kg with the vinyl-ether containing PPI-1040 for 28 days (n=6). Our results show that PPI-1040 treatment augmented multiple endogenous PlsEtn species to near wild-type levels in the circulation, and to varying degrees in peripheral organs including the liver, small intestine and skeletal muscle. Although augmentation was not detectable in the brain, PPI-treated mice showed normalization of the hyperactive behavior to wild-type levels (p<0.05) with a strong correlation between behavior and plasma PlsEtn levels observed (R²=0.5). Studies are ongoing to uncover the biology underlying this correlation and to evaluate aged Pex7^{Hypo/Null}

animals for the presence of pathological markers of neurodegeneration. These findings suggest that PPIs are capable of augmenting plasma and tissue PlsEtn levels, correlating with normalization of the behavioral phenotype. PPI-1040 is currently being advanced for clinical evaluation in RCDP patients, designed to provide the first proof-of-concept data that synthetic plasmalogen augmentation is a viable therapeutic approach in humans. The poster will conclude with a brief discussion on the implications for AD, and a summary of the clinical development plan for PPI-1040 including the proposed functional endpoints.

Disclosures: **T.M. Smith:** A. Employment/Salary (full or part-time);; Med-Life Discoveries. **W. Fallatah:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support);; Med-Life Discoveries LP. **D. Jayasinghe:** A. Employment/Salary (full or part-time);; Med-Life Discoveries. **S.A. Ritchie:** A. Employment/Salary (full or part-time);; Med-Life Discoveries. **N. Braverman:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support);; Med-Life Discoveries LP.

Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.21/T1

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

Title: Small peptide inhibition of TDP-43 mitochondrial localization alleviates neurodegeneration and memory loss in an APP transgenic mouse model for Alzheimer's disease

Authors: ***M. HARLAND**¹, J. GAO¹, L. WANG¹, H. FUJIOKA¹, H. ARAKAWA¹, G. PERRY², X. WANG¹

¹Case Western Reserve Univ., Cleveland, OH; ²Col. of Sci., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Alzheimer's disease (AD) is the most prevalent form of dementia in the elderly characterized by the progressive loss of neurons in brain regions critical for cognitive function with hallmark pathological features such as senile plaques and neurofibrillary tangles. Current therapies for AD cannot delay disease progression or neurodegeneration, but instead focus on masking the symptoms. TAR DNA binding protein 43 (TDP-43) proteinopathy is a prominent histological feature associated with the cognitive impairment present in AD. We have previously established that mitochondria are a crucial target of TDP-43 induced neurotoxicity. TDP-43 levels are augmented in the mitochondria of 5XFAD transgenic mice, a widely-used model that recapitulates AD-related phenotype, as well as AD patients and highly colocalize with mitochondria in brain neurons that display TDP-43 proteinopathy. Here, we show that the inhibition of TDP-43 localization to mitochondria protects against the neuronal loss and

behavioral deficits in aging 5XFAD mice. Chronic administration of PM1, a TDP-43 mitochondrial localization inhibitory peptide, alleviates TDP-43 proteinopathy, mitochondrial abnormalities, microgliosis, and neuronal loss without altering the amyloid plaque load well after the onset of symptoms in 12-month-old 5XFAD mice. Furthermore, PM1 attenuates the cognitive and motor dysfunction seen in 12-month-old 5XFAD mice. Remarkably, the onset of mild cognitive impairment was also prevented in 5-month-old 5XFAD mice by chronic PM1 infusion. These data indicate that TDP-43 localization to mitochondria is likely a critical step in AD pathogenesis and that inhibition of this process may be a valuable approach for AD therapeutics.

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Poster

049. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 049.22/T2

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

Title: Preclinical evaluation of senolytic therapies for Alzheimer's disease

Authors: *P. ZHANG¹, M. GOROSPE², M. P. MATTSON²

¹Lab. Of Neurosciences, ²Lab. of Genet. and Genomics, Natl. Institute on Aging, Baltimore, MD

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder to date, with no curative or preventive therapy. Recent findings from animal studies suggest that agents that selectively kill senescent cells ('senolytics') can reduce local tissue inflammation and suppress several age-related diseases. To explore a therapeutic potential of senolytics for AD treatment, we first determined if senescent cells are associated with amyloid β -peptide (A β) plaque pathology in human AD patients and mouse models of AD. Using multiple technical approaches, we found that A β plaque-associated Olig2- and NG2-expressing oligodendrocyte progenitor cells (OPCs), but not astrocytes or microglia, exhibit a senescence-like phenotype characterized by the presence of p21, p16INK4, and senescence-associated β -galactosidase (SA- β Gal) activity. OPCs not associated with A β plaques did not exhibit senescence phenotypes. At the ultrastructural level, the plaque-associated senescent OPCs and associated dystrophic neurites exhibit accumulations of autolysosomes, suggest that senescent OPCs may contribute to neuritic dysfunction and degeneration in the plaque environment. Exposure of cultured OPCs to aggregating A β induced cell senescence. Treatment of APP/PS1 mutant transgenic mice with senolytic agents selectively killed senescent OPCs, and significantly reduced A β plaque

pathology and cognitive deficits. Our findings suggest an active role for OPC senescence in AD pathogenesis, and a potential application of senolytic drugs in this disease.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.01/T3

Topic: C.03. Parkinson's Disease

Title: Impacts of CDNF and MANF on neuronal networks and complex behaviors in zebrafish

Authors: *Y.-C. CHEN, S. SEMENOVA, D. BARONIO, P. PANULA
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Abstract: Neurotrophic factors support growth, maintenance, survival and plasticity of neural systems. They are also therapeutic targets for brain disorders such as psychiatric and neurodegenerative diseases. Unconventional neurotrophic factors, mesencephalic astrocyte-derived neurotrophic factor (MANF) and cerebral dopamine neurotrophic factor (CDNF), are known to protect and restore the loss of dopaminergic neurons in the animal models of Parkinson's disease. However, the regulation of dopaminergic neurogenesis in both developing and adult brain remains unclear. The aim of this study was to investigate the effects of *cdnf* and *manf* on neurotransmitter systems in the zebrafish brain. We generated zebrafish knockout mutants lacking functional *cdnf*, *manf* as well as both *cdnf* and *manf* using the CRISPR/Cas9 mediated mutagenesis. The KO mutants were vital, showed no gross morphological phenotypes and grew normally to adulthood. We analyzed the brain neurotransmitter systems including the catecholaminergic, serotonergic, histaminergic and GABAergic systems by qPCR, HPLC and immunohistochemistry. The dopaminergic and serotonergic systems were mainly intact in either *cdnf* or *manf* KO fish, whereas a defect of the dopaminergic neurons was observed in the double-knockout mutant brains. The brain histamine level was lower in adult *cdnf* KO fish than that in the WT siblings. Remarkably, an alteration of the GABAergic system was found in the *cdnf* KO and double-KO mutants. Shoaling behavior and social preferences were significantly different between *cdnf* KO fish and their wild-type siblings. Moreover, *cdnf* KO fish were abnormally susceptible to pentylentetrazole-induced epilepsy. This may be related to the observed abnormally low expression of GABAergic markers in *cdnf* KO fish. These results suggest that the roles of *cdnf* and *manf* in the brain are not restricted to effects on the aminergic systems but also extend to regulating fast-acting neurotransmitter systems. Thus, these factors are likely to function in a broad spectrum of neuronal circuits and brain disorders.

Disclosures: Y. Chen: None. S. Semenova: None. D. Baronio: None. P. Panula: None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.02/T4

Topic: C.03. Parkinson's Disease

Support: University of Utah

Title: Striatal-mediated motor and cognitive function in the DJ-1 KO rat model of Parkinson's disease

Authors: *D. GIANGRASSO¹, T. M. FURLONG², K. A. KEEFE³

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Abstract: The novel DJ-1 knockout (KO) rat models the loss of function mutation of DJ-1 responsible for one form of autosomal recessive Parkinson's disease (PD). DJ-1 KO rats present progressive dopamine (DA) cell body death in substantia nigra pars compacta between 4-8 months of age. As motor deficits emerge before the significant loss of DA cells, this mutation may yield a period of DA neuron dysfunction preceding cell death that may contribute to cognitive impairments early in PD. However, DJ-1 KO striatal integrity and function are largely uncharacterized. We therefore assessed cellular and molecular markers as well as striatal-mediated behavioral task performance in male DJ-1 KO rats and wild-type (WT) controls at 4, 6, and 8 months of age. Experimenters were blinded to genotype during training, testing, and data analysis. Inter-rater reliability was established for behavioral task scoring. On both the tapered balance beam and open field tests, there was no difference between DJ-1 KO and WT performance at 4 months. At 6 and 8 months, however, DJ-1 KOs made significantly more motor errors than controls. DJ-1 KO rats exhibited less anxiety than WT rats at 6 and 8 months on the light-dark box anxiety test. We also assessed action outcome (AO) and stimulus response (SR) associations underlying instrumental learning, a cognitive function impaired in human PD patients and other models of partial striatal DA loss. Both DJ-1 KO and WT rats displayed intact AO control over behavior at all ages. Surprisingly, neither group transitioned to SR control over behavior at any time point. This suggests an age effect, as WTs 4 months and older did not transition to SR control over behavior, whereas prior literature indicates that WT rats <2 months of age do. We also assessed markers of monoamine innervation in dorsal striatum and prefrontal cortex. Dopamine transporter binding densities in the dorsomedial and dorsolateral striata of DJ-1 KO rats did not differ from WT controls at any time point. *Preprotachykinin* mRNA expression, which is sensitive to partial DA loss and altered phasic DA signaling, was lower in the DJ-1 KO dorsal striatum than WTs at all time points. The binding density of serotonin

transporters (SERT) was higher in DJ-1 KO rats than WT rats at 4 months in the orbitofrontal, cingulate, and prelimbic cortices. There was also an age effect, whereby SERT binding densities in WT rats increased across 4 to 8 months, while DJ-1 KO binding densities did not change. Taken together, these data suggest disruption of DA signaling and striatally-based function prior to the onset of DA terminal loss in striata of DJ-1 KO rats, as well as alterations in serotonergic innervation from frontal cortical regions.

Disclosures: D. Giangrosso: None. T.M. Furlong: None. K.A. Keefe: None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.03/T5

Topic: C.03. Parkinson's Disease

Support: NIH NINDS Grant R01NS082565
MJFF Grants 11380 and 11380.01

Title: Analysis of neuromuscular degeneration and regeneration in PINK1 knockout rats

Authors: A. M. RIZWAN, L. J. MCMEEKIN, S. K. BARODIA, M. V. KING, N. K. MOKHA, R. B. CREED, *M. S. GOLDBERG

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Abstract: PTEN induced kinase 1 (PINK1) targets dysfunctional mitochondria for degradation via autophagy, and loss-of-function PINK1 mutations cause autosomal recessive Parkinson's disease (PD). PINK1 knockout (KO) rats model key features of PD including mitochondrial dysfunction, locomotor deficits, and alpha-synuclein aggregates in multiple brain regions. Our behavioral and electrophysiological analyses of PINK1 knockout rats at various ages shows normal function until the acute onset of near complete hind limb paralysis (paraparesis) that begins between 6 and 7 months of age and coincides with reduced sciatic nerve compound motor action potential amplitude. Unlike animal models of amyotrophic lateral sclerosis (ALS) that appear behaviorally similar, PINK1 KO rats have no loss of lower motor neurons and surprisingly, after weeks of near complete hind limb paralysis, PINK1 KO rats regain normal ambulatory function. We hypothesize that dysfunction or degeneration of pre-synaptic axon terminals at neuromuscular junctions of PINK1 KO rats causes the onset of hind limb paresis and that re-innervation from collateral nerve terminals causes the surprising recovery of motor function 4-8 weeks after onset. We predict that PINK1 KO hind limb muscle fibers atrophy during denervation. We further hypothesize that denervation followed by re-innervation from collateral nerve terminals coincides with alterations in muscle fiber morphology or myosin heavy chain fiber type. To better understand the mechanisms of neuromuscular degeneration and

regeneration in PINK1 KO rats, we used immunofluorescence to analyze the slow twitch (Type I) muscle fibers and fast twitch (Type IIa and Type IIb) muscle fibers in 10 micron transverse frozen sections of tibialis anterior and gastrocnemius muscles from wild-type and PINK1 KO rats at ages before, during and after paraparesis. Preliminary analysis indicates age-dependent abnormalities in the muscles of PINK1 KO rats consistent with denervation atrophy followed by re-innervation. This work advances the characterization of PINK1 KO rats, which can provide important insight into the mechanisms by which PD-linked loss-of-function mutations in PINK1 cause dysfunction and neurodegeneration. Our results also suggest that the unusual spontaneous recovery phenotype of PINK1 KO rats may be useful to study mechanisms of repair and regeneration that can lead to functional locomotor recovery.

Disclosures: **A.M. Rizwan:** None. **L.J. McMeekin:** None. **S.K. Barodia:** None. **M.V. King:** None. **N.K. Mokha:** None. **R.B. Creed:** None. **M.S. Goldberg:** None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.04/T6

Topic: C.03. Parkinson's Disease

Support: MJFF GRANT 4219720

Title: Six month-old LRRK2 G2019S knock-in mice do not express motor learning deficits on the rotarod task

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Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene represent the most common genetic form of Parkinson's disease, with the G2019S mutation being the most prevalent. Multiple rodent models have been developed that express this mutation to advance the understanding of the behavioral and physiological basis of LRRK2 Parkinson's disease. A concern about LRRK2 rodent models is that motor impairments associated with Parkinson's disease are not consistently observed. For example, some studies have reported significant impairments in motor performance at 6 months while others report no impairments until ≥ 10 months of age. Furthermore, while many studies examine motor learning in animals in a single-day task, few studies look at how these animals learn across multiple days. To determine whether motor impairments were present at 6 months in our knock-in model and to test if LRRK2 mice would show impairments in motor learning across days, we tested 6 month-old LRRK2 C57CL/B6-G2019S knock-in mice (Taconic Farms) (n=9) and C57CL/B6 WT controls (n=7) in

a motor learning task across 4 days over 2 weeks. Though we observed a significant effect of day on the mean latency to fall in both groups (repeated-measures ANOVA, $F=5.27$ $p=0.004$) this was largely mediated by the increased fall latency between days 1 and 2 (post-hoc paired t-test, LRRK2: $t=4.91$, $p=0.004$, WT: $t=2.72$ $p=0.026$), indicating that both groups learned the task. We observed no significant differences between LRRK2 and WT animals ($F=0.147$, $p=0.71$) or an interaction between animal group and day ($F=0.164$, $p=0.918$). This suggests that motor learning is not impaired in 6 month-old LRRK2 G2019S knock-in mice. These data are consistent with data from a previous study that we conducted using 5 month-old LRRK2 G2019S BAC mice (Jackson Laboratories). In this study, no motor impairments were observed compared to WT in mean latency to fall (Wilcoxon Rank Sum test, $p=0.06$, $n=10$ LRRK2, $n=10$ WT), though this study did observe differences in sleep behavior. The absence of a motor performance difference between G2019S LRRK2 and WT controls supports the claim that gross motor deficits, as measured by the rotarod, are not present at 6 months of age across multiple animal models and suggests that behavioral changes at this age, if present, are subtle.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.05/T7

Topic: C.03. Parkinson's Disease

Support: NCN grant OPUS13 2017/25/B/NZ7/02406
NCN grant OPUS2 2011/03/B/NZ7/05949

Title: Mice with genetically evoked selective loss of noradrenergic system as a possible tool to study presymptomatic phase of Parkinson's disease

Authors: *G. KREINER¹, K. RAFA-ZABLOCKA¹, A. JURGA¹, J. BARUT¹, M. BAGINSKA¹, R. PARLATO^{2,3}, I. NALEPA¹

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Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disorder, characterized by an increased production of oxygen free radicals leading to alteration of the cellular constituents and subsequent dopaminergic cell loss within the region of substantia nigra (SN) and ventral tegmental area (VTA). However, it is well known that PD is associated not only with dopaminergic transmission. Examination of human brain tissues revealed that noradrenergic

cell loss in the region of locus ceruleus (LC) may proceed and is even greater than dopaminergic degeneration of SN/VTA. The aim of this study was to determine whether genetically evoked, selective loss of LC neurons may negatively influence the dopaminergic system. We applied the conditional inactivation of the gene encoding transcription factor TIF-IA (essential for the regulation of rRNA synthesis) by the Cre-loxP system to induce selective loss of noradrenergic neurons which was achieved by expressing Cre recombinase under dopamine beta-hydroxylase (DBH) promoter. Resulting TIF-IA^{DBHCre} mice were born at expected rates, viable but showed clear signs of noradrenergic innervations failure e.g. ptosis, reduced locomotor activity, growth retardance and shorten life span. The complete, selective loss of noradrenergic neurons was confirmed by immunofluorescent staining with the anti-tyrosine hydroxylase (TH) antibody in 12-week-old mutant mice. The number of TH positive cells was not changed in the region of SN/VTA of these mice. Nevertheless, we have noticed that lack of the noradrenergic transmission leads to enhanced expression of various markers associated with neurodegeneration within dopaminergic system: slight upregulation micro- and astroglial markers as revealed by Western Blot, enhanced level of oxidative stress, upregulation of many pro-inflammatory proteins as visualized by protein arrays, and positive signal of FluoroJadeC immunostaining (a fluorescent marker commonly used to label degenerating neurons). Moreover, the analysis of expression profiling performed on the mRNA extracted from SN/VTA region showed changes in many transcripts related to PD. If we provide additional evidences that prolonged, selective noradrenergic degeneration impairs dopaminergic system functioning, mice with ongoing neurodegeneration of LC neurons may become a valuable tool for study presymptomatic phase of PD. As for today, there are no experimental studies on a possible long-term negative impact of progressive noradrenergic degeneration on other neurotransmitter systems, despite of clinically observed concomitant loss of SN/VTA and LC neurons in PD.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.06/T8

Topic: C.03. Parkinson's Disease

Title: Generation of embryonic cell line knock-out for NQO1 for animal pre-clinical model for Parkinson's disease

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Abstract: Parkinson's disease (PD) has been associated with metals, pesticides, neuroleptics and other factors that can induce the disease. However, what induces the idiopathic degeneration of dopaminergic neurons that contain neuromelanin is still unknown. There is a consensus in the scientific community that different mechanisms are involved in PD, such as the formation of alpha-synuclein oligomers, mitochondrial dysfunction, protein degradation dysfunction, neuroinflammation, reticular and oxidative stress. Being these mechanisms part of a vicious cycle that eventually leads to neurodegeneration. Currently, several pre-clinical models have been proposed for PD based on the use of exogenous neurotoxins without obtaining significant results, which can be explained due to the use of exogenous molecules that do not exist in the brain, which does not reproduce what occurs in the brain. Because the event of degeneration occurs extremely rapidly and extensively affecting areas of the brain that are not unique to the nigrostriatal system Aminochrome has been documented as a pre-clinical model of PD. This molecule is formed during the oxidation of dopamine and has been shown to induce mitochondrial dysfunction, dysfunction in protein degradation, alpha-synuclein aggregation, reticulum stress and oxidative stress. However, there are neuroprotective pathways that result in the oxidation of dopamine to aminochrome leading to the formation of neuromelanin. One of these is the reduction of aminochrome to leukoaminochrome by the enzyme DT-diaphorase, the only flavoenzyme to catalyze the reduction of quinones to hydroquinones, expressed both in neurons and in astrocytes avoiding all the neurotoxic pathways of the aminochrome. This neuroprotective role of DT-diaphorase against aminochrome may explain why the oxidation of dopamine to neuromelanin occurs normally. The use of knock-out animals for DT-diaphorase injected with aminochrome will be a new preclinical model that will help to study the mechanisms of the disease and the development of new drugs for PD. This is why the failures that have been seen in the deficiency of significant results from preclinical to clinical studies and the development of new pharmacological therapies can be overcome once the appropriate preclinical model using endogenous neurotoxic is found that is directly involved this disease.

Disclosures:

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.07/T9

Topic: C.03. Parkinson's Disease

Support: NIH/NIEHS 1R01ES024745
Michael J. Fox Foundation

Title: Neurogenic inflammation resulting from expression of constitutively activated NLRP3 in mesencephalic dopamine neurons

Authors: *K. VON HERRMANN, E. M. MARTINEZ, F. L. ANDERSON, A. L. YOUNG, M. C. HAVRDA

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Abstract: Neuroinflammation is a well-characterized pathophysiology associated with the progression of Parkinson's disease (PD). Characterizing the cellular and molecular basis of neuroinflammation is critical to understanding its impact on the incidence and progression of PD and other neurologic disorders. Inflammasomes are intracellular pattern recognition receptors capable of initiating and propagating inflammation, and have been well-characterized in the innate immune system. Specifically, the NLRP3 inflammasome is a cell-intrinsic pro-inflammatory mediator capable of initiating inflammation in response to sterile cellular stressors, such as reactive oxygen species and misfolded protein products. NLRP3, a key component of the NLRP3 inflammasome complex, is a multi-functional NOD-like receptor (NLR) containing a highly conserved NACHT domain along with an n-terminal pyrin domain and a c-terminal leucine rich repeat domain. Multiple polymorphisms in the catalytic NACHT domain have been previously associated with human inflammatory disorders, including Cryopyrin-associated periodic syndromes (CAPS) spectra. Reports from our lab and others indicate that in animal models of PD, Nlrp3 is required for neuroinflammation and nigral cell loss. In the CNS, NLRP3 expression is readily observed in microglia. Additionally, neuronal NLRP3 expression has been observed in cultured cells and in distressed neurons following cerebral infarction. We recently observed NLRP3 expression in dopaminergic neurons of the mesencephalon in tissues obtained from PD patients and inducible expression of NLRP3 in tyrosine hydroxylase-positive differentiated LUHMES cells. To determine whether neuronal expression of NLRP3 contributes to the development of neuroinflammation and/or neurodegeneration, we bred mouse lines expressing inducible NLRP3 harboring activating NLRP3 polymorphisms associated with the CAPS spectra with mice expressing CRE-recombinase under the control of the dopamine transporter. We conducted an extensive, longitudinal study assessing behavioral and serologic endpoints at multiple time points over an 18-month period. Findings from our collective work are consistent with reports by others indicating age-dependent elevation of NLRP3 expression in the CNS and indicate that hyperactivation of NLRP3 in dopamine neurons may contribute to neuroinflammation and the progression of PD symptomatology in mice.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.08/T10

Topic: C.03. Parkinson's Disease

Support: Department of Medicine, University of Florida

Title: An experimental rodent model of Parkinson's disease: Quantitative measurements of rigidity, gait, and iron deposition

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Abstract: Parkinson's disease (PD) is one of the most common neurodegenerative conditions in the elderly affecting over one million people in the United States. The disease is characterized by motor disability related to increased muscle tone/rigidity, abnormal gait and posture, and balance impairment. The objective of this current work is to create a reliable quantitative model of PD, where motor impairments can be measured, and experimental therapies can be tested. Stereotaxic injections of 3 μ l of 2.5 μ g/ μ l 6-hydroxydopamine (OHDA) targeting midbrain Substantia nigra pars compacta (AP -5.16 mm; L 2.0 mm; D 7.8 mm) were made using a microinjection pump at the rate of 0.5 μ l/min. We have previously reported physiological indices of the development and measurement of spasticity/rigidity following spinal cord and traumatic brain injuries. Thus, the velocity-dependent ankle torques, time-locked triceps surae EMGs, and H-Reflex rate-depression were assessed to quantitate measures of rigidity using methodology that we developed and reported previously. The 3-D kinematic and footprints analyses of gait, rotorod and ladder tests were also employed to chart locomotor disabilities. Moreover, MRI (7.0 T, MR Solutions) was used to standardize the accuracy of injection sites (T1/T2-weighted), detect iron deposition in the substantia nigra (QSM), and assess the integrity of the nigrostriatal dopaminergic pathways (DTI/GQI). Our data to date indicate that animals receiving 6-OHDA injections exhibited progressive and significant increases in velocity-dependent rigidity accompanied by time-locked elevated triceps surae EMGs. This elevated rigidity was also mirrored by the loss of rate-dependent depression in the reflex pathways (H-Reflex rate depression) that served the rigid/spastic muscles in these rodent subjects. Moreover, toxin injected animals also exhibited significant alterations in parametric measures of gait, and balance performance. These observations are consistent with the progressive loss of inhibition known to contribute significantly to the progressive development of increased and inappropriate muscle activation during passive muscle lengthening phases of locomotion. MRI studies in progress are assessing toxin-induced alterations in a comprehensive array of anatomical changes, iron deposition in the substantia nigra, and the integrity of the nigrostriatal dopaminergic pathways. Progressively, these studies aim to increase our understanding of the neurobiology of this experimental model of PD, and to utilize this as a platform for testing the safety and efficacy of new iron chelating therapy which has an opportunity for quick translation.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.09/T11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Laboratory of Motor Control and Neuromodulation of University of Chile
Fondecyt N° 1151478
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NuMIND Millenium Nucleus N° NC130011

Title: Electrophysiological patterns as a biomarker of Parkinson's disease

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Abstract: The diagnosis of Parkinson's Disease (PD) is based on clinical criteria. This approach might be inaccurate, making it difficult to differentiate PD from other parkinsonisms. Therefore, isolating biomarkers facilitating the clinical diagnosis might be critical. Here, we propose a sensitive and reliable electrophysiological biomarker, which would allow to detect the pathological changes characteristic of PD. We used awake Sprague Dawley male rats (n=6) at rest with unilateral 6-hydroxydopamine (6-OHDA) lesion while in-vivo recording electrophysiological signals from 5 areas of the motor circuit (primary sensory (S1), primary motor (M1), ventral medial agranular cortex (AGvm), dorsolateral striatum (DLS) and thalamus ventral posterolateral nucleus (VPL)) of both hemispheres. We used the unilateral 6-OHDA lesioned rats as a parkinsonian model, where the injured hemisphere stands for the PD condition and the uninjured hemisphere was used as a control. After obtaining representative signals of each area, we extracted patterns with characteristic behaviors from their estimated power spectral density (PSD). First, we evaluated the changes of these spectral patterns in the control and lesioned hemisphere. Then, we evaluated the changes of this spectral patterns in the lesioned hemisphere before and after a putative neuromodulatory treatment. Finally, we determined a biomarker made up of 3 metrics obtained from the spectral patterns found. The proposed biomarker allowed to differentiate between control and lesioned hemisphere. Furthermore, our biomarker could distinguish between untreated and treated parkinsonian conditions. These

results suggest that the proposed biomarker could be helpful to diagnose PD and bring new treatments to the right patients.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.10/T12

Topic: C.03. Parkinson's Disease

Support: CNPq Universal - 475531/2012-4
CAPES Scholarship

Title: Stem cell transplantation and physical exercise in a model of Parkinson's disease

Authors: *A. A. OLIVEIRA, JR, J. D. C. HURTADO, J. P. B. SANCHEZ, C. RODRIGUES, M. R. WINK

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Abstract: Introduction: Current therapies for Parkinson's disease (PD) temporarily relieve symptoms but seldom modify the underlying pathology. Disease-modifying strategies such as stem cell transplantation (SCT) and physical exercises have shown highly overlapping neuroprotective and immunomodulatory properties. **Objective:** The aim of this study was to assess the efficacy of combining mesenchymal SCT and treadmill exercise training for counteracting motor and cognitive alterations induced by 6-hydroxydopamine (6-OHDA). **Methods:** Male Wistar 6-OHDA unilaterally injured rats were randomized to receive either none or one of three treatments: 4-week treadmill training; 2×10^5 human adipose-derived mesenchymal stem cells transplanted within the striatum ipsilateral to the lesion; or both treatments. At the end, performances on the footfault test, novel object recognition, and passive avoidance tests were assessed. **Results:** While the three approaches significantly reduced the footfault-induced rotational behavior and improved limb coordination and paw placing, exercise only and the combined use of SCT plus exercise were superior. Paradoxically, treadmill training was associated with impaired long-term recognition memory, anxiety-like behavior and enhanced fear response to an aversive memory. Interestingly, these enhanced avoiding and anxious behaviors reverted with the combined use. **Discussion:** Overall, this study ratifies the therapeutic potential that SCT and exercise hold for addressing the motor deficits seen after dopaminergic depletion, and open questions as to the best approach to target the associated cognitive dysfunctions. It is possible that the stressing effect of a shock-motivated treadmill training could have canceled any beneficial effect in areas vulnerable to stress (memory circuits)

while otherwise have had potentiating effects in activity-engaged basal ganglia circuitry (motor circuits). More studies are needed to verify the real potential of these two strategies and their combined use in the management of the motor and non-motor symptoms of PD secondary to dopaminergic dysfunction.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.11/T13

Topic: C.03. Parkinson's Disease

Title: Encephalitic infection with mosquito-borne alphavirus causes long-term neurodegenerative consequences consistent with Parkinsonism in surviving host

Authors: *C. BANTLE¹, A. PHILLIPS¹, S. ROCHA¹, K. OLSON^{1,2}, R. TJALKENS¹
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Abstract: Viral infections of the central nervous system of vertebrate animals are known to induce long-term neurodegenerative consequences, including protein-aggregation, oxidative-stress, mitochondrial dysfunction and neuronal death. Clinical and experimental evidence suggests that neuroinvasive infections reproduce features of many neurodegenerative diseases, including Parkinson's disease (PD). Here, we determined the effects of western equine encephalitis virus (WEEV) infection on PD-relevant brain regions in an outbred mouse model of non-lethal encephalitis. Mice (CD-1) were experimentally infected with recombinant WEEV expressing rescued from reporter proteins constructs. Following intranasal inoculation, all animals became infected, and WEEV spread along the neuronal axis in a pattern that mimicked the Braak-staging system of PD in humans, revealed a broad distribution of RFP-expressing WEEV throughout the CNS, caused pronounced neurobehavioral abnormalities, marked glial activation and loss of dopaminergic neurons in the SNpc. To prevent mortality, mice were treated with polyclonal antibodies to the WEEV E1 glycoprotein at 12 and 48 hours post-infection, whereupon they cleared WEEV and remained viable for at least two months. Levels of viral replication were monitored by in situ bioluminescence imaging for the entire eight weeks of infection. Surviving mice displayed significant DA cell loss, glial cell activation, proteinase K resistant α -synuclein protein aggregation and a gene expression profile consistent with PD-like pathology. Taken together, these results support that mosquito-borne alphavirus infection can produce lasting parkinsonian features in CD-1 mice, and can be used in existing transgenic models of PD for therapeutic and mechanistic research.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.12/T14

Topic: C.03. Parkinson's Disease

Title: AAV-mediated progerin expression in the rat midbrain as a model of age-related Parkinson's disease

Authors: *I. M. SANDOVAL^{1,3}, B. F. DALEY¹, J. H. KORDOWER^{4,5}, F. P. MANFREDSSON^{2,3}, T. J. COLLIER⁶

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Abstract: Aging has been singled out as the major risk factor for Parkinson's disease (PD). Indeed, previous work from our laboratories support the view that aging and PD exist along a biological continuum in which aging actively produces a vulnerable pre-PD state. However, the means by which aging affects the cellular and molecular mechanisms leading to neurodegeneration remains elusive. Recently, the protein responsible for the genetic premature aging disorder Hutchinson-Gilford progeria syndrome was identified. This protein, named progerin ("pro-aging"), is a mutant version of the filament protein Lamin A, a major component of the nuclear lamina. Expression of progerin induces many phenotypes, such as abnormal nuclear shape, loss of peripheral heterochromatin and increased DNA damage, leading to cellular senescence. In order to better understand the effects of aging on the health and survival of dopaminergic neurons of the *substantia nigra*, the cells most vulnerable in PD, we aim to induce cellular senescence by locally manipulating the expression of progerin in the midbrain of rats using recombinant adeno-associated viral vectors (rAAV). In a proof-of-concept experiment we delivered rAAV-progerin or rAAV-mCherry (control vector) into the substantia nigra of young adult (3 month old) rats. Ten weeks later tissue was collected and processed for histological analysis. Immunostaining for progerin confirmed successful viral transduction and proper nuclear localization. Immunostaining for tyrosine hydroxylase, a marker of substantia nigra dopaminergic neurons, revealed severe neuronal loss. This suggests that progerin overexpression can accelerate the aging process, sensitize nigral DA neurons and ultimately induce neurodegeneration in young rats. Ongoing studies are aimed at further characterizing this model,

including and a progerin dose response, the analysis of nuclear morphology, alterations in epigenetic markers, quantification of DNA damage, as well the temporal course of neural degeneration. We believe our new model will provide a very valuable tool to help inform the role of aging in the etiology of PD, as well as other age-related neurodegenerative disorders.

Disclosures: **I.M. Sandoval:** None. **B.F. Daley:** None. **J.H. Kordower:** None. **F.P. Manfredsson:** None. **T.J. Collier:** None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson's Disease

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Title: PET studies with a rat model of PGJ2-induced neuroinflammation exhibiting parkinsonian-like pathology

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Abstract: Although many reports support the importance of the cyclooxygenase pathway in Parkinson's Disease (PD), the underlying mechanism and the role of prostaglandins in neurodegeneration remains to be explored. Prostaglandin D2 is the most abundant prostaglandin in the brain, increases the most under pathological conditions, and is quickly converted to the highly neurotoxic prostaglandin J2 (PGJ2). Our earlier efforts to develop a mouse model of neuroinflammation (NI) revealed that repeated PGJ2 microinjections into the *substantia nigra* (SN) led to Parkinsonian-like pathology with reduction of dopaminergic neurons in the SNpc, activation of microglia/astrocytes and impaired gait and balance. To improve our ability to perform longitudinal quantitative PET imaging, we sought to establish a similar NI model in rats. Here, we report our initial findings in rats unilaterally lesioned with PGJ2 using μ PET imaging to characterize microglial activation and dopaminergic neuronal loss.

PGJ2 (or vehicle) was injected into the right SN of 18-week old male rats for two weeks (once per week). The rats were then analyzed for: i) microglia activation with TSPO- μ PET using [¹¹C]PK11195 and Iba1 immunostaining and ii) dopaminergic neuronal loss with DAT- μ PET using [¹¹C]PE2i (pre-synaptic neurons), D₂R- μ PET using [¹¹C]raclopride (post-synaptic neurons), tyrosine hydroxylase immunostaining and motor deficits (cylinder test), over the course of 45 weeks post-surgery.

Compared to the vehicle controls, PGJ2-treated rats exhibited significantly higher PK uptake

indicating increased microglial activation. At week 4, the lesioned side of rat brains showed average V_T ratio of 1.55 ± 0.10 for PGJ2 and 1.23 ± 0.16 for vehicle ($P=0.01$). At week 8, the PK average V_T ratio dropped to 1.37 ± 0.15 for PGJ2 ($P=0.02$) while vehicle returned to baseline. The PGJ2-treated rats exhibited also motor deficits concomitant with dopaminergic neuronal loss in the impaired SN. At week 14, PE2i BP_{ND} ratios were 0.81 ± 0.05 for PGJ2 and 0.97 ± 0.04 for vehicle ($P=0.02$) while no PGJ2 related alterations in RAC binding were found. Dopaminergic neuronal damage in PGJ2 lesioned rats remained at 17-20% till the end of study (45 weeks). In conclusion, we have developed a Parkinsonian-like rat model of NI. Our data reveal sustained microglial activation with subsequent moderate loss of pre-synaptic dopaminergic neurons in response to PGJ2 detected with PK- μ PET and PE2i- μ PET, respectively. This model will be used to test pharmacological interventions for reversal of NI as a strategy to prevent or delay the progression of PD-like pathology. The model can also aid in testing novel PET ligands of neuroinflammation.

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Poster

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Title: Link between mood regulation and circadian rhythm in midbrain dopaminergic neurons in a 6-hydroxydopamine-injected mouse model of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive degeneration of dopaminergic (DAergic) neurons particularly in the substantia nigra (SN). PD patients are known to suffer from a variety of non-motor symptoms such as mood disorders and sleep disturbances with motor deficits. We have recently demonstrated that REV-ERB α , a circadian nuclear receptor, serves as a key molecular link between mood regulation and circadian nature of DAergic system in the midbrain. Therefore, we aimed to examine how circadian rhythm is related to mood regulation in a mouse model of PD. A neurotoxin 6-hydroxydopamine

(6-OHDA) was injected into left dorsal striatum to induce PD-like symptoms, and mood-related behaviors were assessed at two time points: dawn (circadian time [CT] 22-02 hr) and dusk (CT 10-14). While vehicle-injected mice exhibited daily oscillation of mood-related behaviors, these rhythmic patterns were disappeared in 6-OHDA-injected mice with increased anxiety- and depressive-like behaviors only at dawn, not at dusk. 6-OHDA treatment also induced circadian disturbances of locomotor activity and body temperature. Administration of 6-OHDA eliminated daily rhythmic expression of tyrosine hydroxylase, a rate-limiting enzyme of DA synthesis, with DAergic neuronal loss in both SN and ventral tegmental area (VTA). Interestingly, a local administration of REV-ERB antagonist, SR8278 into midbrain recovered mood disorders shown in 6-OHDA-injected mice by lessening anxiety- and depressive-like behaviors with partial alleviation of motor deficits. Taken together, these results suggest a novel therapeutic potential of REV-ERB α in circadian rhythm-related mood disorders of PD patients.

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Poster

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Title: Effects of sleep disruption on stress, nigrostriatal markers, and behavior in a chronic/progressive MPTP model of Parkinson's disease

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Abstract: The objective of this study was to determine if sleep disruption (**SD**) leads to a greater loss of the dopamine (**DA**) biomarker, tyrosine hydroxylase (**TH**), following chronic/progressive treatment with the neurotoxin, 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (**MPTP**). Sleep complaints are an early clinical marker of neurodegenerative disorders (Chahine et al., 2017). Patients with Parkinson's disease (**PD**) experience sleep disruption, including excessive daytime sleepiness and sleep fragmentation. SD may be associated with, and potentially affects, both motor and non-motor symptoms in PD. We hypothesized that SD is a risk factor in the pathogenesis of PD and that SD would potentiate a greater loss of TH within the nigrostriatal

pathway in those with early PD. We used a progressive/chronic mouse model of PD to test this hypothesis. Mice (C57BL/6J, male, 12 weeks) underwent chronic SD [home cages placed on an orbital shaker (100 RPM); rotations for 10 seconds, every 90 seconds] for 4 weeks (Li et al., 2014), then were injected with vehicle or MPTP for an additional 4 weeks with increasing doses (10, 20, 24, and 32mg/kg, i.p., 5 d/wk) (Churchill et al, 2017). After 4 weeks of SD+MPTP, gait was assessed, and then mice were euthanized for serum corticosterone, brain histology, and western immunoblot analyses. There was a significant decrease in the plasma corticosterone levels in the MPTP group, an increase in the SD group, and a return to the control (CTL) levels in the SD+MPTP group ($p < 0.02$). Optical density and protein expression levels for TH in the striatum (terminals) and substantia nigra pars compacta (DA cell counts) revealed a 55-78% and 38% decrease, respectively, in both the MPTP and SD+MPTP compared to both the CTL and SD groups ($p < 0.03$). Dopamine transporter protein expression increased in the striatum in the MPTP vs CTL group ($p < 0.04$), which decreased in the SD+MPTP group towards the CTL values. Vesicular monoamine transporter-2 protein expression increased in the SD+MPTP and SD only group compared to the CTL group ($p < 0.05$). Measures of gait, including brake time, stride length/time, showed greater changes in the SD+MPTP vs the MPTP group, which were unrelated to the loss of nigrostriatal TH. These data suggest that SD, prior to administration of MPTP, has effects on serum corticosterone and gait, independent of brain markers of nigrostriatal degeneration.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

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Topic: C.03. Parkinson's Disease

Support: Saskatchewan Health Research Foundation
Natural Sciences and Engineering Research Council of Canada
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Title: Induction of a unilateral lesion with a selective adenosine A1 receptor agonist produces motor deficits and neuronal loss in the substantia nigra of Wistar rats

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Abstract: Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), resulting in progressive motor dysfunction. Traditional animal models for Parkinson's disease include lesioning of the SNc or nigro-striatal pathway using substances toxic to dopaminergic neurons, such as 6-hydroxydopamine (6-OHDA) or rotenone. Although these substances produce robust parkinsonian symptoms in rats, these models are not necessarily translational to the human disease and don't allow us to investigate the progressive early stages of the disease. Adenosine signaling has been implicated in multiple aging-related neurodegenerative disorders including stroke, Alzheimer's disease, and Parkinson's disease. Our lab has recently shown evidence of prolonged adenosine A1 receptor (A1R) activation causing neurodegeneration, demonstrated by significant neuronal death in the hippocampus, substantia nigra, and other important brain areas following 48h or 7 day intraperitoneal (i.p.) injection of rats with the A1R agonist N6-cycloptyladenosine (CPA). Female Wistar rats were laterally lesioned with CPA in the nigro-striatal pathway. Both 3 and 6 weeks following lesioning, a battery of testing was performed to characterize motor function. Post-mortem analysis of the SNc using immunohistochemistry was then performed to explore the effects of lesioning on the dopaminergic neuron population. Lesioned rats showed motor deficits in motor behavioural tests and immunohistochemistry assays showed significantly reduced tyrosine hydroxylase staining on the lesioned side of the SNc. Taken together, these results indicate that lesioning the nigro-striatal pathway with CPA induces parkinsonian symptoms which may give us further insight into the role of adenosine in the development of Parkinson's disease.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

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Program #/Poster #: 050.17/U1

Topic: C.03. Parkinson's Disease

Support: UK Dementia Research Institute, Imperial College, London, U.K.

Title: Acquisition and reversal of visual discrimination learning in MPTP-treated C57BL/6J mice

Authors: *T. HEIKKINEN¹, J. P. JARVENPÄÄ^{2,1}, M. KOPANITSA^{1,3}, A. SHATILLO¹, J. RYTKÖNEN¹, L. REMES¹, J. T. PUOLIVALI¹

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Abstract: Injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to mice cause a significant dopaminergic neuronal loss, biochemical and cellular changes and behavioural

symptoms similar to those observed in individuals with Parkinson's disease. The c-Abl tyrosine kinase inhibitor nilotinib was previously shown to protect dopaminergic neurons and rescue motor deficits in MPTP-treated mice. We explored if a) MPTP treatment affected acquisition and reversal of visual discrimination learning in a translational touch screen test and b) whether administration of nilotinib before and after MPTP injections would prevent putative cognitive deficits. MPTP or saline were injected on days 0 and 1 in two doses of 20 mg/kg daily at 3 h intervals. Nilotinib or vehicle were given once daily from day -5 to day 8. Testing in touch screen chambers started on day 16. Locomotor activity and measures of touch screen pretraining performance were similar in the three experimental groups (control, MPTP, MPTP+nilotinib). Further, there were no statistically significant inter-group differences in the numbers of trials and errors in the pairwise visual discrimination task, in which mice learned to differentiate between two similar grid images until 80% correct response rate. However, when data from MPTP and MPTP+nilotinib groups were combined (due to the absence of obvious nilotinib effect), mice from this pooled MPTP group required slightly but significantly more trials to achieve the criterion than control animals. When the correct and incorrect visual stimuli were reversed, the reversal learning curves and all reversal learning parameters were similar in all groups of mice, including comparisons of control and pooled MPTP groups. Furthermore, all groups retained the relearned visual discrimination memory equally well. We then explored performance of these animals in tapered beam test at 2.5 months after MPTP/saline treatment. Surprisingly, we did not detect a difference between control and MPTP-treated mice in beam crossing times and in the number of foot slips. ¹H-MRS performed at 5 months did not reveal increased glutamate and decreased lactate levels in the striatum typically seen at ~12-35 days post MPTP treatment. HPLC analysis of striatal samples done after ¹H-MRS imaging showed decreased levels of dopamine and its metabolites in MPTP-treated animals, although changes were smaller compared to historical data at earlier periods after MPTP challenge. These results suggest gradual time-dependent recovery of biochemical and behavioural disturbances in MPTP-treated mice.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

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Program #/Poster #: 050.18/U2

Topic: C.03. Parkinson's Disease

Support: COFAA-IPN fellowship

Title: Memory disabilities in rats with dopaminergic denervation in globus pallidus

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Abstract: Parkinson's patients besides of characteristic motor disabilities show well-recognized nonmotor symptoms as depression, dysautonomia, sleep problems and dementia. Particularly dementia is preceded by subtle memory dysfunctions and both are been suggested to be produced by degeneration of dopaminergic mesocorticolimbic innervation originating in the ventral tegmental area. However early manifestations of cognitive impairments are possibly linked to dopaminergic dysfunction in frontal cortex and caudate nucleus. In this regard, dopaminergic projections originating in substantia nigra compacta innervate globus pallidus (GP) in primate and rat. Memory malfunctions have been reported by lesions or temporal inactivation of GP in human, cat, and rat. So in this work, we search for alterations in memory tasks as object recognition, object location and temporal order recognition in rats with depletion of dopamine in GP. With this purpose, 4 groups of rats were uni and bilaterally injected in GP with 6-hydroxydopamine or vehicle and one month later memory tasks and locomotor activity were tested. We found a significative reduction in recognition indexes in the three task in both unilateral and bilateral lesioned rats without alteration in locomotor activity. Temporal order recognition index decreased 56 %, novel object recognition index diminished 87%, and object location reduced more than 95 %. These results imply the engagement of failures in dopaminergic innervation of GP in dysfunctions of recognition memory particularly the processing of temporal order information as has been reported in early parkinsonians patients.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

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Topic: C.03. Parkinson's Disease

Title: Implication of nigral dopaminergic lesion and repeated L-dopa exposure in neuropsychiatric symptoms of Parkinson's disease

Authors: *S. LOIODICE¹, H. WING YOUNG², B. RION², B. MÉOT², P. MONTAGNE², A.-S. DENIBAUD², R. VIEL³, C. DRIEU LA ROCHELLE²

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Abstract: In addition to motor impairments which constitute the cardinal symptoms of Parkinson's disease (PD), different neuropsychiatric manifestations (e.g. cognitive impairment, psychosis, anxiety) can be observed. It has been suggested that some of these symptoms may stem from the loss of nigral dopaminergic (DA) neurons. However, previous data reported that repeated exposure to DA medication may also play an important role in aberrant neuroplasticities associated with non-motor manifestations. In this study, we sought to investigate the contribution of nigral DA cell loss, repeated exposure to DA medication and the combination of both to the development of neuropsychiatric symptoms observed in PD.

A bilateral stereotaxic injection of 6-OHDA (2.6 $\mu\text{g}/\mu\text{L}$) into the substantia nigra pars compacta (SNc) was performed in rats. A set of animals was repeatedly administered with L-dopa (20 mg/kg/day) and benserazide (5 mg/kg/day) over a period of 10 days starting from day 11 post-lesion. Behavioral testing was performed on week 3 post lesion using the novel object recognition (NOR), the elevated plus maze (EPM), the social interaction (SI) test and amphetamine induced hyperlocomotion (AIH).

The immunohistochemical analysis revealed a significant nigral lesion with 35.2% of DA cell loss in 6-OHDA rats versus sham. Consistently with previous data, no motor impairment was observed after such partial lesion of the SNc. However, a significant deficit in the NOR was observed in lesioned rats whether they were chronically exposed to L-dopa or not. This deficit was reversed by an acute treatment with L-dopa/benserazide (12.5 mg/kg and 15 mg/kg respectively) in rats that were not previously exposed to L-dopa. A significant deficit was also observed in lesioned rats in the EPM after SNc lesion with no impact of chronic or acute exposure to L-dopa. No difference was observed in the SI test or in the AIH assay.

This study provides new insights into the neuropathophysiology associated with neuropsychiatric symptoms of PD. Our data suggest that the loss of nigral DA neurons per se may underlie some of these manifestations while repeated exposure to L-dopa had a limited impact on the behavioral endpoints assessed in this study in a context of partial nigral loss.

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Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

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Topic: C.03. Parkinson's Disease

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CAPES

FAPESC (PRONEX - Project NENASC)

FINEP (IBN-Net #01.06.0842-00)

Title: The intranasal MPTP administration in rats: An animal model to study nociceptive alterations in the early stages of Parkinson`s disease

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Abstract: Pain is a non-motor alteration present in a large proportion of Parkinson`s disease (PD) patients and has a significant negative impact on their quality of life. Although this symptom occurs secondarily to the motor alterations of PD, about 40% of PD patients experience pain in the early stages of PD. Considering that the pathophysiology is not well understood and there is not an appropriate management for this symptom, it is important to define these alterations in rodent models of PD. Therefore, our aim was evaluated the nociceptive alterations followed the intranasal administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a model of the early stages of Parkinson`s disease. For this, 32 male Wistar rats (90 days) were treated with a single i.n. infusion of MPTP (1 mg/nostril) or saline. At 7, 14 and 21 days later 20 rats (10 per group) were evaluated in von Frey and hot plate tests, and 12 rats (6 per group) were evaluated in acetone and tail flick tests. In another experiment, 24 rats (6 animals per group) also received i.n. MPTP or saline, and 14 days later received a single intraplantar administration of capsaicin (20 µL, 5 mM, right hind paw) or vehicle (0.15% ethanol in saline) and was measured the time spent licking the injected paw, which was considered an indication of nociception. In order to evaluate the motor alterations, 48 rats (8 per group) animals received MPTP or saline and were independently evaluated at 7, 14 and 21 days later in the pole test and cylinder test. The evaluators were blinded with regard to the experimental groups. (CEUA 1454/2017) Our results indicated that the MPTP induces mechanical and hot hyperalgesia at 14 and 21 days after i.n. infusion, and also increases the nociceptive responses followed the intraplantar capsaicin 14 days later. The MPTP administration did not modify the nociceptive responses followed the intraplantar acetone test and increase the latency of response to the tail flick test 14 days later. In relation to motor evaluations, the MPTP did not modify the turn time in the pole test and the rearing behavior in the cylinder. This study demonstrates that intranasal MPTP, an experimental model of early PD, induced nociception alterations in rats earlier than motor disabilities.

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Poster

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Title: Glial-derived inflammatory environment as an outcome of dopamine and glutamate dysregulation in the dorsal striatum of dyskinetic mice

Authors: *M. S. PEREIRA^{1,3}, G. H. D. ABREU², J. ROCCA³, S. HAMADAT³, J. SEPULVEDA-DIAZ³, P. MICHEL³, R. RAISMAN-VOZARI³, E. DEL BEL²
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Abstract: Recent studies have suggested L-DOPA-induced dyskinesia (LID) may be related to an inflammatory environment, which involves glial cells activation in the striatum. This pro-inflammatory environment may result from excessive levels of glutamate and dopamine (DA) released following L-DOPA administration. Our aim was to verify whether L-DOPA treatment in hemiparkinsonian mice increases the levels of astrocytes and microglia and the production of inflammatory cytokines in the striatum and whether DA or glutamate application directly into purified cultured glia generates an inflammatory response. 6-hydroxydopamine-lesioned C57BL/6 mice were treated with L-DOPA (25 mg/kg + Benserazide 10 mg/kg i.p.) for 21 days and had their striatum analyzed by immunohistochemistry. For in vitro analysis, glial cell isolation was performed based on a previously established protocol and stimulated with L-DOPA/DA or glutamate. Hemiparkinsonian mice developed severe axial, limb, locomotor and orofacial abnormal involuntary movements ($X^2(3) = 26.28, p < 0.05$). L-DOPA treatment induced astrocytic activation in the dorsolateral striatum ($F(3, 24) = 26.12, p < 0.05$) and an increase of reactive microglia ($F(3, 24) = 16.33, p < 0.05$). There was also an augmentation in the cytokines TNF- α ($F(2, 15) = 20.37, p < 0.05$), IL-1 β ($F(2, 15) = 14.33, p < 0.05$) and IL-6 ($F(2, 15) = 9.431, p < 0.05$). L-DOPA/DA stimulation in cultured astrocytes (3 and 10 μ M) resulted in cytokines TNF- α ($F(6, 35) = 180.2, p < 0.05$) and IL-6 reduction ($F(6, 35) = 596.4, p < 0.05$). Glutamate stimulation (50 and 500 μ M) generated an increase in GFAP expression ($F(2, 9) = 79.03, p < 0.05$) and TNF- α production ($p < 0.05$). In cultured microglia, DA diminished Iba-1 expression ($F(2, 9) = 8.292, p < 0.05$). Glutamate induced Iba-1 increase ($F(2, 9) = 74.72, p < 0.05$). Finally, the combination of anti-inflammatory compounds capsazepine/cannabidiol (5 mg/kg + 30 mg/kg i.p.) attenuated LID. This effect was, at least in part, via inhibition of the pro-inflammatory cytokine TNF- α production. We conclude that glial activation accompanies cytokine production in dyskinetic mice, and this inflammatory environment might result from an imbalance of glutamate and DA levels acting jointly in glial cells.

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Poster

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Topic: C.03. Parkinson's Disease

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Title: Profiling epigenome-wide DNA methylation and hydroxymethylation after developmental exposure to the toxicant dieldrin, a model of increased parkinsonian toxicity

Authors: J. KOCHMANSKI, S. VANOEVEREN, C. L. SAVONEN, *A. I. BERNSTEIN
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Abstract: Human and animal studies have shown that exposure to the organochlorine pesticide dieldrin is associated with increased Parkinson's disease (PD) risk. Previous work has demonstrated that developmental dieldrin exposure induces a state of "silent" dopaminergic dysfunction, leading to increased susceptibility to MPTP in adult male C57BL/6 mice after developmental dieldrin exposure. However, the mechanism underlying this enhanced toxicity has not been identified. As such, the long-term impact of low-dose, developmental dieldrin exposure on PD risk remains unclear. Here, we utilized an animal exposure model to test the hypothesis that developmental exposure to low-dose dieldrin alters neuronal susceptibility via specific changes in both epigenetic marks and gene expression. For this study, 8-week-old female C57BL/6 mice were exposed to 0.3 mg/kg dieldrin by feeding every 3 days for 30 days prior to mating; dieldrin exposure continued for the duration of gestation and lactation. Pups were then aged to 12 weeks without subsequent exposure to dieldrin. At 12 weeks, midbrain and striatum were dissected and whole brains were fixed from male and female pups from independent litters. Confirming previous results, we observed the same male-specific increase in DAT:VMAT2 ratio that was hypothesized to represent the "silent" dysfunction underlying increased MPTP susceptibility. To test our hypothesis that the mechanism of this "silent" dysfunction is mediated by specific changes in both epigenetic marks and gene expression, DNA and RNA were isolated from midbrain samples, and three next-generation sequencing methods - RNA-sequencing (RNA-seq), reduced representation bisulfite sequencing (RRBS), and oxidative reduced representation bisulfite sequencing (oxRRBS) - were used to measure dieldrin-related gene expression, DNA methylation, and DNA hydroxymethylation, respectively. Contrary to our hypothesis, we did not identify any differentially expressed genes or transcripts by dieldrin exposure (FDR<0.05); however, we did identify significant differentially methylated regions (DMRs) and differentially hydroxymethylated regions (DHMRs) by developmental dieldrin exposure (FDR<0.05). The discordance between the gene expression and epigenetic results

suggests that developmental dieldrin exposure may not directly affect gene expression, but rather establish a poised epigenetic state early in life. The sensitivity of this poised epigenome to additional environmental stimuli may represent an important biological mechanism underlying this “silent” dysfunction affecting the development of later-life PD.

Disclosures: J. Kochmanski: None. S. Vanoveren: None. C.L. Savonen: None. A.I. Bernstein: None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.23/U7

Topic: C.03. Parkinson's Disease

Support: SAF2014-56671-R
USP-BS-APP03/2014

Title: Pleiotrophin overexpression in the 6-hydroxydopamine striatal mouse model of Parkinson's disease: Involvement of neuroinflammation

Authors: *E. GRAMAGE, R. FERNÁNDEZ-CALLE¹, Y. B. MARTÍN², C. PÉREZ-GARCÍA¹, G. HERRADÓN¹

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Abstract: Pleiotrophin (PTN) and Midkine (MK) are cytokines involved in nerve tissue repair processes and in survival and differentiation of dopaminergic neurons. Their expression levels are upregulated in the nigrostriatal pathway of Parkinson's Disease (PD) patients and in animal models of PD. Also, they have been proposed as modulators of neuroinflammation after different stimulus. Now, we aim to characterize the dopaminergic denervation and the glial activation in the Striatum after intra-striatal injections of the Parkinsonian toxin 6-hydroxydopamine (6-OHDA) in PTN and MK GEMMs (Genetic Engineered Mouse Models). In immunohistochemistry studies, we found that the injection of 6-OHDA induced a significant decrease of tyrosine hydroxylase (TH) staining in the Striatum of Wild type (WT) mice. The lack of endogenous PTN or MK didn't show an effect in the dopaminergic denervation induced by 6-OHDA, as observed in PTN and MK knock-out (PTN^{-/-} and MK^{-/-}) mice. However, this degeneration induced by 6-OHDA was totally absent in mice with transgenic PTN overexpression (PTN-Tg). Regarding neuroinflammation, an extremely high reactive astrogliosis was found in WT mice treated with 6-OHDA, especially in the area where the dopaminergic axons were degenerated. Microglia was also activated, but in a lesser extent than astrocytes. The same pattern was found in PTN^{-/-} and MK^{-/-} mice, while in PTN-Tg mice, the glial activation

induced by 6-OHDA was significantly reduced. These evidences demonstrate that PTN overexpression protects against the damage on dopaminergic nigrostriatal pathway, and suggest an involvement of neuroinflammation in the protective actions of PTN.

Disclosures: **R. Fernández-Calle:** None. **Y.B. Martín:** None. **C. Pérez-García:** None. **G. Herradón:** None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.24/U8

Topic: C.03. Parkinson's Disease

Support: UNAM PAPIIT-DGAPA IN215114
UNAM PAPIIT-DGAPA IN219617
PAPCA-Iztacala UNAM 2016-13

Title: Lipid peroxidation in different cerebral nuclei induced by Manganese inhalation as a Parkinson's disease model

Authors: **D. RODRÍGUEZ-NOLASCO**¹, **A. GUTIÉRREZ-VALDEZ**¹, **E. MONTIEL-FLORES**¹, **V. ANAYA-MARTÍNEZ**¹, ***M. AVILA-COSTA**²

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Abstract: In the nervous system, the brain is especially susceptible to oxidative damage due to its high oxygen consumption, its high-energy demand and high abundance of lipids and fatty acids. Some metals like Iron, Copper and Manganese (Mn) seem to have an important role in oxidative stress, leading eventually, in some cases to neurodegeneration. In Parkinson's disease (PD), oxidative stress has received major attention due to the potential of Dopamine to oxidize and form and other reactive oxygen species. Therefore, the objectives of this work was to evaluate the motor coordination of control animals as well as the animals that have inhaled the mixture of Mn compound, likewise analyze lipid peroxidation in five brain nuclei; substantia nigra (SN), striatum (Str), globus pallidus (GP), hippocampus (HIP) and motor cortex (MC). 40 male CD-1 mice were used. Before Mn exposure the animals were trained for motor coordination tests for a week, and then divided into two groups. The control group inhaled deionized water for one hour, twice a week for 5 months, while the experimental group inhaled the mixture of Mn chloride (0.04 M and Mn acetate (0.02 M. After five months, the mice were sacrificed, the brains were extracted and the nuclei of interest dissected, for lipid peroxidation determination by thiobarbituric acid (TBARS) technique.

Our results showed, that exposure to the Mn mixture produces alterations at the behavioral level, being like the symptoms in PD patients. The MC and HIP were structures that do not show

differences in lipid peroxidation levels. Str, PG and SN are vulnerable structures to lipid peroxidation producing higher concentrations of MDA. These results in conjunction with other experiments using the same model provide a more general view of the Mn of neurotoxicity and its implications in the nigrostriatal pathway as a reliable PD experimental model.

Disclosures: **D. Rodríguez-Nolasco:** None. **A. Gutiérrez-Valdez:** None. **E. Montiel-Flores:** None. **V. Anaya-Martínez:** None. **M. Avila-Costa:** None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.25/U9

Topic: C.03. Parkinson's Disease

Support: CONACYT Grant 287959

Title: Intranigral iron accumulation in rat using ferrous sulfate released from a nanostructured silica matrix as a model of Parkinson's disease

Authors: ***R. OSORNIO**¹, E. ORTIZ-ISLAS², M. SALINAS-MOROTE³, G. CHÁVEZ-CORTES³, D. SILVA-ADAYA³, M. CALVILLO-VELASCO³

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Abstract: Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by deficit in dopaminergic neurotransmission of the nigro-striatal ascending pathway. One of the main causes that lead dopaminergic neuronal death of *substantia nigra pars compacta* (SNpc) is the increase in the intraneuronal content of iron (Fe). From some years ago, the use of local drug release systems using nanomaterials as carriers has been markedly increased, in particular, silicon dioxide (SiO₂) in its different nanometric structures has been used as a biocompatible reservoir of various neurological drugs to deliver them in the central nervous systems of Wistar rats. In the present work, we propose to use ferrous sulfate (FeSO₄) released from a nanostructured SiO₂ matrix to produce a localized, gradual and sustained iron release as a function of time. For that, first Fe-SiO₂ and SiO₂ nanoparticles were synthesized using the sol-gel method by the hydrolysis-condensation of TEOS in medium acid (H₂SO₄). FeSO₄ was added *in situ* during the silica's preparation. In order to know their final properties, the obtained materials were characterized by infrared and ultraviolet-visible spectroscopies, and X-ray diffraction techniques. Typical signals of silica and ferrous sulfate were observed by infrared spectroscopy. Similarly, peaks corresponding to iron salt were identified by x-ray diffraction. These results suggest that ferrous sulfate did not undergo structural changes during the Fe-SiO₂ sample preparation. After that, male Wistar rats (280-310g) (n=7) were administered with 4 µg/3 µL of

Fe-SiO₂ nanoparticles/s.s. through unilateral stereotactic intranigral microinjection. Our preliminary results showed a significant increase ($P < 0.05$) in the evaluation of circling behavior, seven days after of Fe-SiO₂ nanoparticles injection, when was compared to the group treated only with 4 μg/3 μL of SiO₂, which are of order of sham group. The animals group intranigral administered with 400 nmol of FeSO₄ presented significative ($P < 0.01$) increase in circling behavior. 24 h later the animals were sacrificed (n=3) by perfusion and the brain was removed; then, the histological analysis showed intraneuronal iron accumulation and loss of tissue cytoarchitecture using the Prussian blue staining in the group administrated only with Fe-SiO₂ and severe necrotic tissue damage in the group administrated with FeSO₄ was observed. In this sense, we consider that this model will be useful in the study of the neurochemical bases in the formation of intraneuronal iron deposits in patients with PD, which is a causal factor of overproduction of free radicals, oxidative stress and neuronal death.

Disclosures: R. Osornio: None. E. Ortiz-Islas: None. M. Salinas-Morote: None. G. Chávez-Cortes: None. D. Silva-Adaya: None. M. Calvillo-Velasco: None.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.26/U10

Topic: C.03. Parkinson's Disease

Support: NIH Grant T32 DC009401 (Broadfoot)
NIH Grant R01 DC014358 (Ciucci)
NIH Grant R21 DC016135 (Kelm-Nelson)
UW Department of Surgery (Ciucci)
UW Department of CS&D Emma Allen Scholarship (Broadfoot)

Title: Cognitive and vocal communication is impacted by social isolation in a Parkinson's disease rat model

Authors: *C. K. BROADFOOT, M. R. CIUCCI, C. A. KELM-NELSON
Univ. of Wisconsin Madison, Madison, WI

Abstract: Parkinson Disease (PD) is a complex, progressive neurodegenerative disease characterized by limb motor, cranial sensorimotor motor, and non-motor features including anxiety, depression, and cognitive dysfunction. Social function and quality of life are negatively impacted by communication deficits, and the presence of anxiety and depression in PD. The well-established *Pink1* *-/-* rat model shows sensorimotor dysfunction including vocal deficits with onset and progressive pathology similar to humans. The central hypothesis for this study is that social isolation further contributes to vocal degradation, and enhancing social experience

will slow the progression of vocal communication deficits, improve cognitive ability, and decrease overall levels of anxiety and anhedonia. Further, we hypothesize that neurochemical content in associated brain regions will be altered by these social conditions. To test this in a preliminary study, twelve male *Pink1*^{-/-} rats were randomly assigned into 3 groups: 1) socially-isolated, which were housed individually, 2) pair housed, which were housed with a cage-mate and 3) socially-enriched, which were housed with a cage-mate and underwent social enrichment (SE). SE involved grouping rats in a larger ‘socialization’ cage with another pair of cage mates 5x per week. To measure acoustic and non-acoustic parameters of vocal communication abilities, ultrasonic vocalizations (USVs) were recorded at 2 (baseline), 4, 6, and 8-month time points. At the final time-point, all animals were assessed for cognitive skills (novel object recognition test), anxiety levels (elevated-plus maze), and presence of anhedonia (sucrose preference test). A mixed model repeated measures two x three ANOVA revealed significant differences in cognitive abilities but not in levels of anxiety or anhedonia between social conditions. Trends showed that peak frequency was higher in isolated *Pink1*^{-/-} rats compared to socialized animals, suggesting a potential impact on functional communication. After testing, animals were euthanized and brain tissue from the ventral tegmental area, medial prefrontal cortex, and the substantia nigra will be assayed for dopamine, norepinephrine, and serotonin levels using HPLC. This study suggests that social experience may affect behavioral outcomes in a translational rat model PD.

Disclosures: **C.K. Broadfoot:** A. Employment/Salary (full or part-time);; University of Wisconsin-Madison. **M.R. Ciucci:** A. Employment/Salary (full or part-time);; University of Wisconsin-Madison. **C.A. Kelm-Nelson:** A. Employment/Salary (full or part-time);; University of Wisconsin-Madison.

Poster

050. Parkinson's Disease: Animal Models and Associated Behaviors

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 050.27/U11

Topic: C.03. Parkinson’s Disease

Title: A non-human primate model of parkinsonian freezing

Authors: **Y. HAN**^{1,2}, **E. H. BEDOY**^{2,3,4,5}, **N. CHEHADE**³, ***D. KASE**³, **T. M. PEARCE**⁶, **R. S. TURNER**^{2,3,4,5}

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Pittsburgh, Pittsburgh, PA; ⁶Dept. of Pathology, Univ. of Pittsburgh Med. Ctr., Pittsburgh, PA

Abstract: One symptom of Parkinson’s Disease (PD) is freezing, which is defined as the sudden inability to initiate or continue a movement. Although it is well known that the basal ganglia-

thalamocortical circuit is altered in PD, very little is known about the neural correlates of parkinsonian freezing. We trained monkeys to perform a choice reaction-time reaching task before and after being rendered hemiparkinsonian by intracarotid administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The reach task requires the monkey to: 1) hold its hand for a random delay at a visually occluded start position by the monkey's side; 2) reach outward to one of two possible visually-cued targets; and 3) after delivery of food reward, return the hand to the start position. Following MPTP, the animal was still able to perform outward reaches, albeit with slowed reaction times and movement durations. However, freeze-like behaviors occurred when the monkey was required to self-initiate a return to the visually occluded start position. 'Freeze' trials were defined as a >1.5 sec delay of the first peak hand speed after reward delivery for a successful outward reach. This inability to return occurred only after MPTP administration and it occurred after 100% of the reaches prior to experimental manipulation of the task parameters. Allowing vision of the start position substantially decreased the freeze proportion from 100% to 15.9% of total ($p < 0.001$, chi-squared test), and this effect lasted long (>19 days) after the start position was again hidden from the monkey (Freeze proportion=27.5%). This suggests that freezing is exacerbated by the absence of visual cues or visual cue-dependent memory. Freeze proportion decreased further to 3.4% of total trials when the return movement was also rewarded ($p < 0.005$, chi-squared test), suggesting a direct influence of motivation. The proportion of freeze trials also increased across time within a session ($p < 0.01$, t-test), indicating that fatigue may also increase the likelihood of freezing. Visual cues, motivation and fatigue also modulate freezing in human patients with PD, which parallels observations in our monkey model, thereby strengthening the model's potential for elucidating the neural correlates of freezing. The ability to manipulate the degree of freezing will facilitate our ability to compare neural activity between movement and freezing states.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.01/DP05/U12

Topic: C.03. Parkinson's Disease

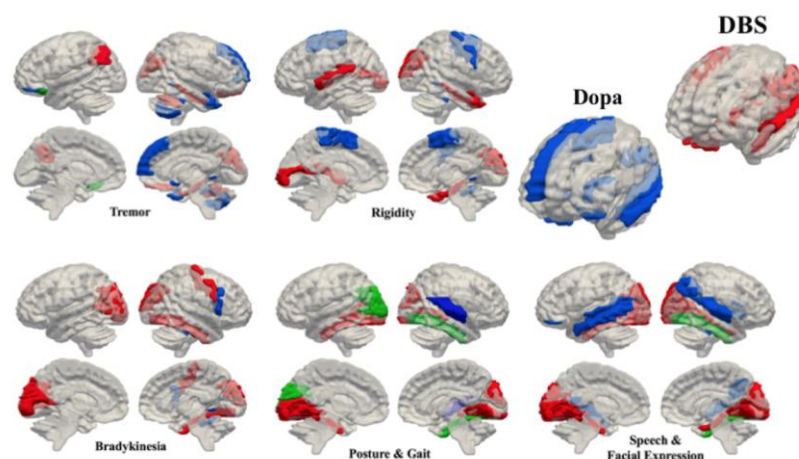
Support: Brain Research Trust (BRT)
Parkinson's Appeal

Title: Distinct network hubs identify functional connectivity patterns predictive of treatment response to subthalamic stimulation in Parkinson's disease

Authors: *C. WU¹, J. MULLER¹, T. FOLTYNIE², P. LIMOUSIN², L. ZRINZO³, H. AKRAM³
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Abstract: Distinctive resting-state functional connectivity (FC) pattern is associated with varying degrees of l-DOPA response in patients with advanced Parkinson's disease (PD). To explore the FC pattern associated with response to deep brain stimulation (DBS), 19 patients underwent 3-Tesla resting-state functional magnetic resonance imaging in the ON-medication state prior to subthalamic DBS. Whole brain FC was measured between regions-of-interest (ROIs) defined by the Automated Anatomical Labeling (AAL) atlas. For both l-DOPA and DBS, several general linear models ($p < 0.05$) were used to assess the relationship between all FC measures and clinical improvement in Unified Parkinson's Disease Rating Scale motor scores (UPDRS-III) - including tremor, bradykinesia, rigidity, gait/posture, and speech subscores. Graph theory metrics were analyzed. An ROI was defined as a 'hub' if it was in the top 20% of at least three of the following graph theory measures: betweenness centrality, clustering coefficient, local efficiency, and degree. The identified hubs reflect increased network integration relative to clinical response.

In line with previous studies, the supplementary motor area was identified as a hub for response to l-DOPA, for which a cerebellar hub was also noted. Response to DBS was characterized by hubs within the temporal and occipital lobes. While sharing common themes, benefit for each motor symptom was associated with distinct networks - highlighted by differences in hubs. The results highlight the importance of evaluating the entire brain network, as regions outside of the typically-studied cortico-basal ganglia-thalamic network may play important roles. Hubs identified in associative and visual networks suggest the importance of intact compensatory mechanisms in patient response to treatment. This is the first study to our knowledge to identify the whole-brain network properties of FC in advanced PD as it relates to both medical and surgical interventions.



Network hubs for motor response to medical and surgical therapies. For overall improvement in UPDRS-III [top right] as well as for each symptom subscore; *blue* regions represent hubs for response to l-DOPA; *red* regions indicate hubs for response to DBS; and *green* regions indicate hubs for response to both l-DOPA and DBS.

Disclosures: J. Muller: None. T. Foltynie: None. P. Limousin: None. L. Zrinzo: None. H. Akram: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.02/V1

Topic: C.03. Parkinson's Disease

Title: Freezing of gait in challenging activities: Analysis of freezing during backward gait whilst playing tennis

Authors: *B. BERGMANS, P. GINIS, A. NIEUWBOER
Rehabil. Sci., KU Leuven, Leuven, Belgium

Abstract: We present a 58-year-old patient diagnosed with Parkinson's disease since eight years. Four years ago, he developed mild freezing of gait (FOG) which disappeared completely after the increase of dopaminergic medication. Two years ago, he started to experience sudden episodes of FOG leading to falls only when running backwards whilst playing tennis. No other circumstances were associated with FOG and in the clinic no FOG could be observed. Due to these FOG-episodes he had to quit playing tennis. The addition of amantadine 2x100mg/day improved FOG considerably. The residual freezing did not lead to falls anymore, so that he could resume playing tennis, his favorite pastime. The patient's motor performance was analyzed in a movement analysis laboratory while wearing Inertial Movement Unit sensors (OPAL-system) during tennis, forward and backward gait and a FOG provoking 360-degree turning-in-place test.¹ During forward and backward gait under both normal and dual-task conditions, no FOG could be triggered, even not at the end-of-dose. When playing tennis, a FOG-episode was registered following festination during backward gait. During the 360-degree turning-in-place test a very short freezing episode was also detected and the FOG-ratio confirmed that the patient was indeed an incipient freezer, according to published criteria. This case highlights that FOG assessment in the clinic can be challenging and needs to be adapted to the patient's subjective FOG-provoking circumstances, enabling early FOG-treatment adjustments. Sensor-based evaluation in a laboratory can be a helpful complementary test, as it allows personalized assessment. **References** 1. Mancini et al. The clinical significance of freezing while turning in Parkinson's disease. *Neuroscience*. 2017 Feb 20;343:222-228. 2. Nieuwboer et al. Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon. *Mov Disord*. 2013 Sep 15;28(11):1509-19. 3. Nutt et al. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol*. 2011 Aug;10(8):734-44. 4. Giladi et al. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. *Mov Disord*. 2008;23 Suppl 2:S423-5. 5. Giladi. Medical treatment of freezing of gait. *Mov Disord*. 2008;23 Suppl 2:S482-8. 6. Nonnekes et al. Freezing of gait: a practical approach to management. *Lancet Neurol*. 2015 Jul;14(7):768-78.

Disclosures: P. Ginis: None. A. Nieuwboer: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.03/V2

Topic: C.03. Parkinson's Disease

Title: Auditory habituation in persons with Parkinson's disease after a socially evaluated cold pressor

Authors: *A. F. ZAMAN, E. L. STEGEMÖLLER
Kinesiology, Iowa State Univ. Dept. of Kinesiology, Ames, IA

Abstract: In healthy young adults acute stress has been shown to impair working memory. Moreover, auditory habituation is positively correlated with working memory and is reduced following acute stress. Auditory habituation is thought to promote cognitive efficiency by neurologically filtering out task irrelevant information. However, there is limited research examining the effects of stress on working memory and auditory habituation in persons with Parkinson's disease (PD). The objective of this study was to determine how an acute stressor such as the socially evaluated cold-pressor (CP) affects auditory habituation in persons with PD. Ten persons diagnosed with mild to moderate PD participated in an electroencephalography (EEG) paired-click paradigm before and after the socially evaluated CP. During the paired-click paradigm participants listened to pairs of identical auditory clicks with a duration of 20ms and an inter-click interval of 500ms. Eighty pairs of clicks were presented with a 7 second interval. The p50 ratio (peak-to-peak method) for the Cz electrode was analyzed after filtering with a 10-45Hz bandpass. During the socially evaluated CP participants were video recorded and told that their expressions were going to be evaluated while they placed their least affected hand in 2°C water for 90 seconds. Perceived stress (Likert scale: 1-10) and saliva cortisol were measured following the CP task, and before they completed the control paired-click paradigm. A two-tailed paired t-test ($\alpha = 0.05$) was used to compare the means. The results revealed that perceived stress was higher following the stressor (5.6 ± 2.7) compared to baseline (2.75 ± 2.9). While there were no significant differences we also found that the p50 auditory habituation ratio was lower during baseline (0.495 ± 0.19) compared to the CP (0.73 ± 0.40), and cortisol levels were greater after the stressor (0.25 ± 0.23) compared to baseline (0.19 ± 0.16). The CP was successful in causing physiological and perceptual levels of stress to rise. The CP decreased auditory habituation suggesting that decreased auditory habituation may be an underlying cause of stress's negative effect on executive functioning in persons with PD.

Disclosures: E.L. Stegemöller: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.04/V3

Topic: C.03. Parkinson's Disease

Title: Altered diffusivity measures of the hypothalamus in Parkinson's disease patients with autonomic dysfunction

Authors: *C. ROUSSEAU¹, M. SKLEROV², N. BROWNER², Y. LEE^{1,3}, A. BOUCAUD⁴, J. PRIETO⁴, M. STYNER⁴, E. DAYAN^{1,3}

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Abstract: The presence of autonomic dysfunction in Parkinson's Disease (PD) contributes adversely to patients' quality of life, and is strongly predictive of prognosis and survival. Autonomic symptoms are regulated through the central autonomic network, where the hypothalamus plays a key regulatory role. Here, we investigated whether white matter integrity of the hypothalamus differs in PD patients with high and low autonomic dysfunction, using diffusion-MRI. Forty-four PD patients were included in the study. All data were obtained from the Parkinson's Progression Markers Initiative (PPMI), an international, multi-center, observational study (<http://www.ppmi-info.org/>). Scores in a questionnaire that assesses autonomic symptoms in PD (SCOPA-AUT) were used to divide patients into those with low (n=22; 9 females; mean age = 55.3 ± 7.0; mean score = 2.7 ± 1.2) and high (n=22; 8 females; mean age = 62.1 ± 7.9; mean score = 18.9 ± 6.4) autonomic symptom burden. Structural MPRAGE scans and diffusion-weighted imaging (DWI) scans were analyzed in all subjects. Preprocessing and quality control of DWI data were performed with DTIPrep, an open-source tool for identification and correction of common diffusion-MRI artifacts. For each patient, the hypothalamus was manually segmented in the individual structural space, and co-registered to the individual DWI space. Diffusivity measures were extracted from the hypothalamus for each patient. Diffusivity measures, extracted from the brainstem, were used to assess the specificity of the results. Our preliminary analysis reveals that relative to patients with low autonomic symptom burden, patients with high autonomic burden showed increased mean (p = 0.01), axial (p < 0.01), and radial diffusivity (p = 0.04) in the hypothalamus. In contrast, we did not find significant group differences in all diffusivity measures extracted from the brainstem. The results reveal consistent differences between patients with low and high autonomic symptom burden in hypothalamic diffusivity measures. Hypothalamic diffusivity may thus potentially be used as an

imaging marker to assist in the identification of therapeutic targets for autonomic dysfunction in PD and monitor the effectiveness of interventions in clinical trials.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.05/V4

Topic: C.03. Parkinson's Disease

Support: Parkinson's Disease Research Society

Title: Gene and protein expression in blood and CSF for biomarker identification in Parkinson's disease patients

Authors: S. QIN, *J. K. NOLT
Northwestern Med. Central Dupage Hosp., Winfield, IL

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting approximately 1 million Americans and 7 million worldwide. Despite the relatively high prevalence of PD in the aging population and the high cost of medication and therapeutic surgery, the diagnostic tools for PD are still limited to parkinsonian symptom observation and/or expensive imaging methods. Unfortunately, by the time motor symptoms are present, patients have already lost at least 60% of dopaminergic neurons. With the advance of molecular detection and analysis technology, substantial efforts have been dedicated to develop *in vitro* molecular diagnostic tools for PD, especially at the preclinical stage of the disease. In this study, we analyzed the expression of 34 candidate genes and 20 proteins in blood and cerebrospinal fluid (CSF) samples collected from PD patients (n=53) and matched control subjects (n=80) to identify potential molecular biomarkers for early detection of PD. Gene expression analysis confirmed previously identified potential biomarkers of PD: SNCA (alpha-synuclein), a major constituent of Lewy bodies, which are the pathological hallmarks of PD, and CTSB (Cathepsin B), a lysosomal enzyme. Recent studies suggest cathepsin B regulates the degradation of alpha-synuclein. SNCA and CTSB are both expressed at lower levels in PD subjects compared to healthy controls. However, we also found ABCA1 (ATP binding cassette subfamily A member 1) demonstrates higher gene expression in PD samples. ABCA1 encodes for a cholesterol efflux pump in the cellular lipid removal pathway and is a major regulator of cellular cholesterol and phospholipid homeostasis. This result suggests an association between cholesterol levels and PD risk. Analysis of cholesterol levels in blood and CSF samples are currently under investigation.

These candidates and their combination could be promising biomarkers for diagnosing PD at the preclinical stage.

Disclosures: S. Qin: None. J.K. Nolt: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.06/V5

Topic: C.03. Parkinson's Disease

Title: Serum ceruloplasmin is associated with impulsivity in people with Parkinson's disease

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Abstract: Background: Parkinson's disease (PD) is considered a multidimensional disorder, which can frequently result in a range of both motor and non-motor symptoms, including cognitive decline and neuropsychiatric complications such as impulsivity. Demographic variables and dopamine D2 agonist medication are known to predispose people with Parkinson's disease (PwP) to be more impulsive. However, it is unknown which PwP are more susceptible to greater trait impulsivity. Given the importance of iron and copper regulation in dopamine homeostasis within the brain, this study aimed to investigate serum ferritin and ceruloplasmin as predictors of impulsivity in PwP.

Methods: Serum iron studies and ceruloplasmin levels were obtained from 214 PwP enrolled in the Australian Parkinson's Disease Registry, and 78 aged-matched controls. Barratt Impulsiveness Scale (BIS-11) measures patient impulsivity, and were obtained from patients in the ON state. Serum iron studies and ceruloplasmin levels were obtained through routine immune-assays. Multivariate general linear models (GLMs), controlling for demographic and medication variables, were used to determine whether or not serum markers associated with impulsivity.

Results: No differences were observable in serum ferritin, transferrin or ceruloplasmin between PwP and controls. However, serum ceruloplasmin was significantly elevated in female PD patients compared with their male counterparts ($p < .000$), and male participants appeared to have significantly greater ferritin levels than their female counterparts ($p < .000$). Only serum ceruloplasmin was significantly associated with total BIS-11 scores, whether a dichotomised (≥ 20 g/L) or continuous variable. GLMs controlled for confounding variables, leaving ceruloplasmin and gender as factors that significantly predict higher BIS-11 total scores, second

order non-planning domain, and first order subscales.

Conclusion: Elevated serum ceruloplasmin levels are associated with heightened trait impulsivity, specifically non-planning impulsivity in PwP. Therefore, serum ceruloplasmin may serve as a specific marker for impulsivity in PD patients, and aid in the identification of individuals more susceptible to harmful behaviours such as pathological gambling.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

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Program #/Poster #: 051.07/V6

Topic: C.03. Parkinson's Disease

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NOMIS foundation FTLD project

Title: Pesticides and the risk of Parkinson's disease in an Egyptian study population

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Abstract: Pesticide exposure is associated with an increased risk of Parkinson's disease (PD). In Egypt, where 40 % of the workforce is employed in agriculture, pesticides are extensively used. Today, Egypt has one of the highest prevalence rates of PD worldwide and still only little is known about possible interactions of defined environmental and genetic risk factors. The aim of the present study was to explore the synergistic interactions between environmental pesticide exposure and polymorphisms in specific genes in the etiology of PD. PD patients (n= 416) and healthy controls (n= 445) were recruited in collaborating Neurology Departments of 6 Egyptian universities (Mansoura, Ain Shams, Assiut, Sohag, Tanta and Zagazig). Participants were assessed with a standardized questionnaire to evaluate past exposure to pesticides and other PD-related environmental factors. DNA of each participant was collected and genotyped for single nucleotide polymorphisms (SNPs) in detoxification-related genes. Pesticide exposure was defined as ever used pesticides at home or at work or if resided in a rural area for more than 50 % of lifetime. PD patients were examined to verify presence of PD (UK brain bank criteria) and to quantify disease severity (Hoehn & Yahr stage). By logistic regression analysis we confirmed typical protective and risk-increasing environmental factors of PD. The investigation of 24 SNPs in 15 detoxification-relevant genes led to the identification of one SNP which is associated with increased risk of PD in pesticide-exposed Egyptians. Additionally, we found one SNP in the same gene which was protective regardless of pesticide exposure. Our study provides further insights into specific risk factors that contribute to the increased prevalence of PD in Egypt and more generally into mechanisms of the gene-environment interplay in the etiology of PD.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Topic: C.03. Parkinson's Disease

Support: Cluster of Excellence "Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB)"

Title: Transcriptomic profiling in midbrains of Parkinson's disease patients

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Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disorder worldwide, affecting up to 2% of individuals aged over 60 years. It is characterized by a pronounced degeneration of dopaminergic neurons in the substantia nigra and the presence of alpha-synuclein aggregates. The incomplete understanding of the pathophysiological mechanisms underlying PD and the limited regenerative capability of neurons complicate the development of curative treatment options. Analyzing the transcriptome of PD brains is a promising strategy to reveal pathophysiological processes underlying the disease and might contribute to the development of novel therapeutic strategies. The aim of the present study is to obtain an exploratory overview on the transcriptomic profile in PD human midbrains. Therefore, we performed the transcriptomic profiling from midbrain tissue of PD patients (n=19) and aged-matched controls (AMC; n=13). Human post-mortem tissue samples were provided by the UKPD Brain Bank. Total RNA was isolated from the fresh-frozen samples, mRNA libraries were prepared (Illumina TruSeq SR cluster Kit v3) and massive parallel sequencing was performed (Illumina HiSeq4000). When comparing the transcriptome of the different cohorts, a total of 133 genes were significantly regulated, of which the vast majority - 126 genes - were upregulated in the PD condition (considering $FDR < 0.1$ and $\log_2fc > \pm 0.5$). Functional annotation revealed a down-regulation of the Dopamine Beta-Hydroxylase (DBH) gene, an important player in dopamine metabolism. Pathway enrichment analyses (performed with DAVID Bioinformatics Resources 6.8) reveal several altered biological processes related to inflammatory response ($p = 1,631E-07$), several pathways related to the immune response (innate immune response, $p = 2,524E-05$; defense response, $p = 5,176E-04$; leucocyte migration, $p = 5,819E-04$), regulation of ERK1 and ERK2 cascade ($p = 8,379E-03$) and response to axon injury ($p = 9,734E-03$). Regulated genes and related pathways will be further explored and confirmed by real-time PCR and Western Blotting. Our findings reveal molecular networks that are likely involved in PD pathogenesis and therefore will contribute to a better understanding of disease mechanisms and putative therapeutic targets.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Topic: C.03. Parkinson's Disease

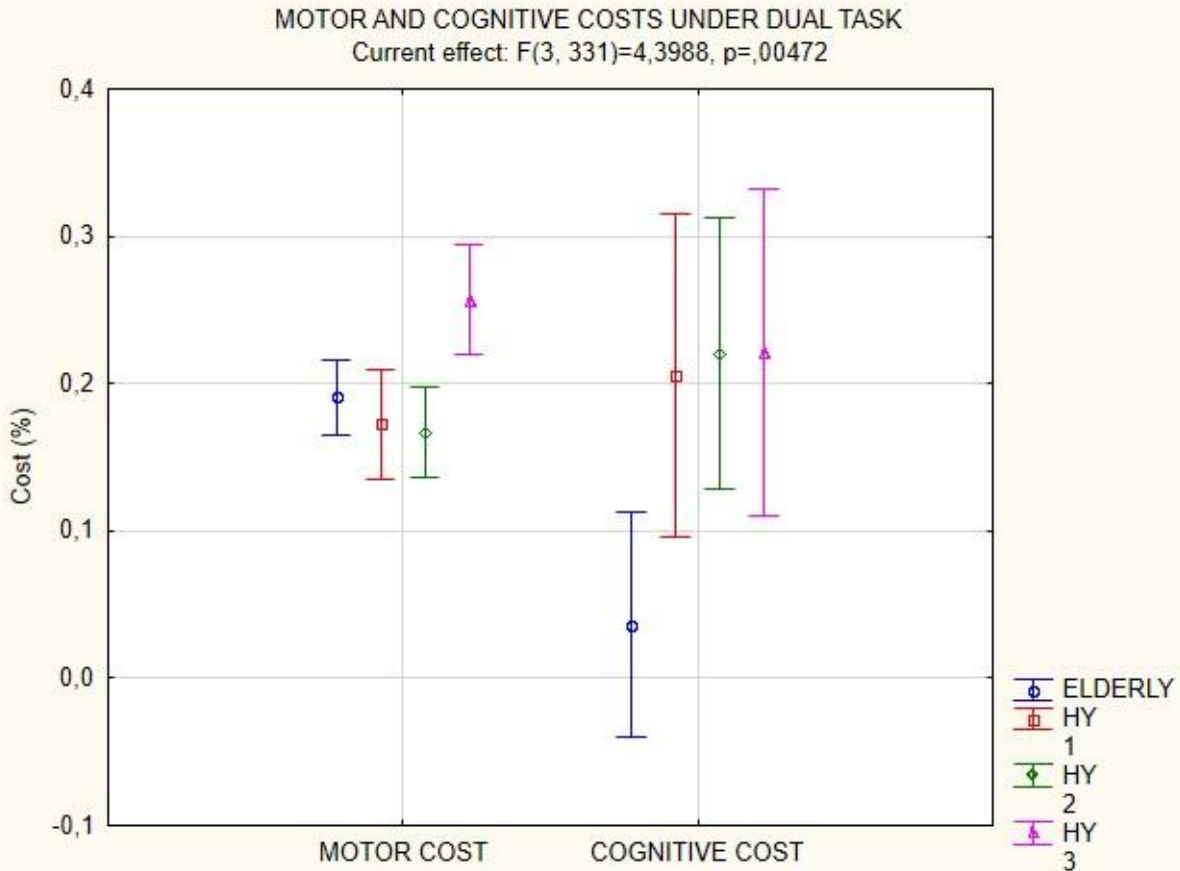
Support: FAPESP

Title: The cognitive cost is higher than motor cost during gait under dual-task in people with Parkinson's disease

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Abstract: Introduction: Impairment in automatic gait associated to dopamine depletion in Parkinson's disease (PD) is considered a crucial factor for reduction in the ability to keep the gait performance under DT condition. Most of the studies has showed the impact of DT condition on the gait performance and few studies has investigated the impact of attention division on cognitive performance. Aim: The aim of this study was to investigate the motor and cognitive cost to divide attention between gait and a concomitant cognitive task in people with PD. Methods: Participated of this study 208 people with PD, in stages 1, 2 and 3 of disease evolution according to Hoehn and Yahr Classification (H&Y), using dopaminergic medication, and 127 elderly paired by age, gender and schooling. All participants were asked to walk for 30 seconds while evocated the higher number of words as possible started with a specific letter, i.e., under dual-task condition (DT). In order to achieve the motor and cognitive baseline performance, i.e., without a concurrent secondary task, the gait performance and verbal fluency were tested under single task (ST) too. The motor cost was calculated by walked distance under ST- walked distance under DT/walked distance under ST. The cognitive cost was calculated by number of words evocated under ST-number of evocated words under DT/ number of evocated works under ST. Results: The ANOVA for repeated measure for costs showed a significative interaction between group (elderly, H&Y 1, H&Y 2 and H&Y 3) and task (motor AND cognitive task) $F(3, 331)=4.3988, p=.004$. The Tukey post-test showed that the cognitive cost for elderly was significantly smaller than motor cost for elderly and cognitive cost for people with PD in 1, 2, 3 H&Y stages (Figure 1). Conclusion: People with PD has more severe impairment to keep the cognitive performance under DT than elderly, even in initial stages of disease evolution. In contrast, motor cost was similar between elderly and people with PD, even in intermediate stage of disease evolution.



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Poster

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Topic: C.03. Parkinson's Disease

Support: Doris Duke Charitable Foundation Clinical Research Scholars Grant

Title: Quantifying Parkinsonian motor symptoms using tablet-based behavioral biomarkers

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Abstract: Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder in which motor symptoms are observed to fluctuate on a rapid timescale. However, current evaluation of PD is subjective and intermittent, with limited reports regarding quantification of short-timescale symptoms. Continuous assessment of motor symptoms in PD could aid the development of closed-loop interventions ranging from automated deep brain stimulator programming and real-time control to tighter scheduling of medication doses. Therefore, we designed a multi-dimensional, continuous motor assay controlled with a stylus-tablet interface to compare the performance of PD patients versus control subjects. **Methods:** 18 PD patients and 13 age-matched controls performed a target tracking task administered on a tablet. The target moved quasi-randomly in a continuous path, and subjects tracked it with a stylus. Motor performance was quantified using seven metrics such as tremor magnitude, vector error, and distance from the target. The data were analyzed in one-second epochs across six minutes of movement to generate performance profiles. Each patient's measures were compared to the aggregate control data using a Support Vector Machine (SVM) binary classifier, and short timescale symptom scores were defined as the distance of the measures from the SVM hyperplane. Larger distances from the hyperplane suggested more severe symptoms compared to the control performance. Each patient was assigned a mean symptom score for the entire session and this was compared to the clinical-standard Unified Parkinson's Disease Rating Scale (UPDRS) graded by a neurologist on the same day. **Results:** Mean symptom scores of the patients were significantly correlated to their UPDRS (Spearman's correlation, $Rho = 0.60$, $p < 0.008$). Patients were classified as asymptomatic in 19.1% of the session during which time they performed indistinguishably from the control group. Weights given to each of the seven metrics by the SVM classifier varied from patient to patient (Kruskal-Wallis test, $p < 0.001$ in all metrics). **Conclusions:** PD motor behavior varies widely in a patient-specific manner on timescales of seconds and at times resembles control behavior. The differences in metric weights demonstrate the heterogeneity of disease symptoms across patients. Our motor assay quantifies rapid symptom fluctuations, which we are now adopting as behavioral biomarkers for moment-to-moment closed-loop control.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Topic: C.03. Parkinson's Disease

Support: Sloan Research Fellowship

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Title: Characteristics of beta waveform shape in Parkinson's disease detected with scalp electroencephalography

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Abstract: Introduction:

Neural activity in the beta frequency range (~20 Hz) is excessively synchronized in Parkinson's Disease (PD). Previous work has shown that this synchrony can be detected with correlations between beta phase and broad-band gamma amplitude (i.e. phase amplitude coupling, PAC), which are elevated in PD. This has been demonstrated using both invasive intracranial recordings as well as non-invasive, electroencephalography (EEG). Recently, other work, using invasive human recordings, has shown that nonsinusoidal features of beta oscillations, such as peak and trough sharpness ratio and rise and fall steepness, may also characterize PD. Here we investigated if these metrics related to waveform shape can also be detected in PD using non-invasive scalp EEG. We tested whether the shape of sensorimotor beta oscillations differed between PD patients on and off medication, and if these measures correlated with PAC.

Methods:

We analyzed a previously collected dataset of 15 PD patients, on and off medications, and 16 age-matched healthy control subjects. All EEG data were collected at rest. Waveform shape (i.e. sharpness and peak to trough sharpness ratio) were calculated using previously published methods. In brief, time-points of oscillatory peaks and troughs were found for a signal band-passed filtered in the beta frequency range (13-30 Hz). Then the voltage of the raw signal was identified at these time-points. Sharpness was derived from the raw voltage difference around each of these points (i.e. for 5 ms before or after each peak or trough). The sharpness ratio was the ratio of the sharpness for the two extrema.

Results:

Focusing on data from the electrodes closest to motor cortex (C3 and C4), we observed greater sharpness and peak to trough sharpness ratio for patients off compared to on medication ($p=0.0003$ and $p=0.04$ respectively, using a paired t-test). Unlike the previous findings for PAC, beta waveform shape did not differ between patients and healthy controls. We also found a positive correlation between sensorimotor sharpness ratio and PAC both on and off medication (off, $r=0.84$, $p = 5.1e-09$; on, $r=0.70$, $p=1.4e-05$).

Conclusion:

These findings suggest that, in addition to PAC, sharpness and sharpness ratio of motor cortical oscillations differentiate PD on and off medication in EEG. Furthermore, our results suggest that waveform shape might be detecting the same underlying physiological signature as PAC, since the two are highly correlated. Future research will explore beta oscillation burst dynamics in relation to medication state in PD patients.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Topic: C.03. Parkinson's Disease

Support: NIH/NINDS P50 NS062684

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Michael J. Fox Foundation for Parkinson's Disease Research

Title: Cerebral white matter hyperintensity severity is linked to changes in attention and executive function in Parkinson's disease

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Abstract: Objective: Parkinson's disease (PD) patients are at increased risk of developing cognitive impairment. Studies indicate that white matter hyperintensities (WMH), brain lesions apparent on T2-FLAIR MRI scans, could contribute to this impairment, though results have been contradictory¹. In this study, we investigated whether WMH contribute to PD cognitive impairment using a comprehensive neuropsychological battery (Level-II) with domain-specific subtyping².

Methods: We included 85 PD and 20 healthy control participants with MRI and cognitive testing in five domains (attention/working memory, episodic memory, executive, visuospatial and language function). Scans were rated for the presence of deep (DWMH) and periventricular (PVWMH) WMH³. The PD group was subcategorized by WMH severity: PD_WMH- (n=71; DWMH grades 0-1 and PVWMH grades 0-2) and PD_WMH+ (n=14; DWMH grades 2-3 and PVWMH grade 3). Additionally, we used automatically segmented WMH masks and nonparametric permutation testing to calculate lesion probability maps for individual cognitive tests.

Results: We defined domain-specific cognitive impairment as a score ≥ 1.5 SD below age- and education-matched normative values in at least one test in a given domain. The PD group showed significant impairment in all five domains compared to the HC group. Within the PD group, a significantly larger percent of PD_WMH+ than PD_WMH- participants showed impairment in attention/working memory ($p = 0.036$) and a trending larger percent in executive function ($p = 0.059$). At the individual test level, PD_WMH+ participants demonstrated significantly lower performance on the Symbol Digit Modality Test (SDMT) compared to

PD_WMH- participants ($p = 0.025$). A lesion probability map negatively correlating lesion location and SDMT performance for PD_WMH+ versus PD_WMH- revealed a significant cluster adjoining the right superior longitudinal fasciculus (SLF, temporal region).

Conclusions: In this study we demonstrate a relationship between WMH severity and PD attention/working memory impairment. More severe WMH were associated with decreased performance on the SDMT, a test of cognitive processing speed, working memory and executive function⁴, suggesting that WMH may contribute to cognitive slowing. This process might include WMH-driven disruption of the right SLF, a white matter tract thought to be involved in executive function⁵. Future studies could investigate whether treating vascular factors associated with severe WMH decreases the risk of cognitive slowing and impairment in PD.

References: ¹ PMID: 26391185 ² PMID: 22275317 ³ PMID: 3496763 ⁴ PMID: 15947059 ⁵ PMID: 21343896

Disclosures: C. McDaniel: None. M. Shahid: None. T.R. Hendershott: None. L. Tian: None. B. Cholerton: None. K.L. Poston: None. P. Linortner: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.13/V12

Topic: C.03. Parkinson's Disease

Title: Upper limb tremor is predictive of falls in Parkinson's disease

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Abstract: Postural instability leading to falls and injury is an important and disabling feature of Parkinson's disease (PD). Increased rigidity, particularly of the legs and trunk, contributes to postural instability in PD. However, the contribution of tremor to postural instability is less certain even though both resting and postural tremor forms are a common motor problem in people with PD.

Bilateral upper limb postural and resting tremor responses of 51 people with PD and 39 age-matched controls were assessed while they stood on a force plate. Upper limb tremor was assessed using accelerometers attached to the superior aspect of both upper limbs on the index finger. All data were recorded at 100 Hz for 30 s. Clinical falls-risk tests and neurological assessments were also performed. Falls were recorded prospectively over 12 months. Acceleration and force plate center of pressure data were low-pass filtered Butterworth filter (40 Hz). These data and quantified using root mean square.

Falls occurred in 69% of PD and 46% of older people over 12 months. PD fallers had longer disease duration, greater dopamine agonist use, increased freezing of gait, decreased activities of daily living compared to PD non-fallers. PD fallers had worse measures for Tinetti Balance, Gait and Total scores compared to PD non-fallers. There were no differences for the Control groups. Both postural and resting tremor were greater for PD fallers compared to PD non-fallers, Control fallers and Control non-fallers.

There were no differences between Control Faller and Non-Faller groups. Anterior-Posterior (AP) postural sway was greater for PD Fallers compared to Control Fallers and Non-Fallers for both the postural and resting tremor assessment conditions. There were no differences between any groups for mediolateral postural sway.

Linear discriminant function analysis by forward variable selection was used to develop a predictive model of future falls. A combination of postural upper limb tremor RMS, dopamine agonist use and Tinetti total score predicted falls outcome in the Parkinson's group with a sensitivity of 89%, specificity of 69% and accuracy of 82%.

Objective assessment of upper limb tremor distinguishes between Parkinson's fallers and non-fallers and is an important predictor of future falls.

Disclosures: G. Kerr: None. N. White: None. S. Morrison: None.

Poster

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Location: SDCC Halls B-H

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Program #/Poster #: 051.14/V13

Topic: C.03. Parkinson's Disease

Support: NRF-2016R1C1B1009247

Title: Machine learning-based prediction of progressive mild cognitive impairment in Parkinson's disease

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³Dept. of Neurol., ⁴Dept. of Radiology, Yonsei Univ. College of Med., Seoul, Korea, Republic of

Abstract: Background: Patients with Parkinson's disease with mild cognitive impairment (PD-MCI) differ in the rate of cognitive decline and in the chance of subsequent conversion to dementia. To assess the risk of conversion to dementia in patients with PD-MCI at an individual level, we aimed to develop a machine learning-based prediction method using cortical thickness. Methods: Patients with PD-MCI (n=167) were divided into two groups as PD-MCI converters

(n=72) and nonconverters (n=104) according to subsequent diagnosis of dementia (mean follow-up period=38.2 months). For each patient, cortical thickness analysis using three-dimensional T1-weighted magnetic resonance images was conducted. Vertex-wise cortical thickness values were extracted from the clusters with significant group difference (false discovery rate-corrected at $P < 0.05$) and used as potential features, along with clinical variables including age, sex, education, and disease duration. All variables except sex were standardized into Z-scores prior to analysis. For feature selection, Recursive Feature Elimination with Cross-Validation (RFECV) using support vector machine (SVM) was performed with a linear kernel. Results: PD-MCI converters showed significant cortical atrophy in the right middle frontal gyrus and left orbitofrontal gyrus. From the two significant frontal clusters, cortical thickness values at 2935 vertices were extracted. Based on the RFECV, which suggested the optimal feature number of 12, the top 12 vertex-wise cortical thickness values along with age, sex, education, and disease duration were selected as final features. For the PD-MCI converters vs. nonconverters classification, linear SVM using 10-fold cross-validation was performed and resulted in mean accuracy of $71 \pm 13\%$. Conclusions: The current results suggest that an individual-level classification using vertex-wise cortical thickness in bilateral frontal regions along with basic clinical information could be helpful to predict conversion from MCI to dementia in patients with PD.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Program #/Poster #: 051.15/V14

Topic: C.03. Parkinson's Disease

Title: Assessment of bradykinesia can predict cognitive function in Parkinson's disease

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Abstract: Background: Parkinson's disease (PD) is primarily recognized by its motor symptoms, which include bradykinesia, tremor, postural instability and stiffness. However, this condition is also associated with a plethora of non-motor symptoms that are difficult to recognize, including cognitive decline. To this end, PD presents as a clinically heterogenic condition. Despite the adoption of validated clinical assessments for both aspects of PD, there

remains difficulty in correlating motor and non-motor symptom presentation.

Objective: To this end, this exploratory study evaluated the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Dot Slide test (a motor assessment for bradykinesia) with the objective of determining their utility in identifying patient cognitive domain scores.

Methodology: Three-hundred and twelve (312) participants with idiopathic PD were recruited from three Australian Movement Disorder Clinics. To assess bradykinesia, the Dot Slide assessment was administered, requiring participants to slide their forefinger between two large dots (30 mm diameter) placed 300 mm apart for 30 seconds. Dot Slide scores were analyzed as continuous variables, or grouped into tertiles for mean comparison. The MDS-UPDRS and Addenbrooke's Cognitive Exam-Revised (ACE-R) were used to determine disease severity and cognitive function, respectively. Multivariate generalized linear models (GLMs), controlling for demographic and medication variables, were used to determine whether Dot Slide score associated with total or domain cognitive function.

Results: Dot Slide score was significantly associated with MDS-UPDRS II and III, and ACE-R performance ($p < 0.001$). When grouped into tertiles based on Dot Slide score, patients in the lower tertile performed significantly worse in the attention and orientation, fluency, and visuospatial ACE-R domains ($p < 0.05$). Using a GLM, patients in the lowest scoring Dot Slide tertile were predicted to score 85-points on the 100-point ACE-R assessment when controlling for gender, age and medication. Given this predicted ACE-R score, our results show that performance in the Dot Slide assessment can differentiate between patients with normal cognitive function and those with mild cognitive impairment.

Conclusions: The Dot Slide assessment of bradykinesia appears to be a useful indicator of motor function and predictor of cognition in PD. To this end, poor Dot Slide performance could identify patients who are at risk of cognitive impairment and require further assessment.

Disclosures: **A. Jefferson:** A. Employment/Salary (full or part-time);; The Perron Institute for Neurological and Translational Science. **M. Byrnes:** None. **S. Ghosh:** A. Employment/Salary (full or part-time);; The Perron Institute for Neurological and Translational Science. **F. Mastaglia:** A. Employment/Salary (full or part-time);; The Perron Institute for Neurological and Translational Science. **R. Anderton:** A. Employment/Salary (full or part-time);; The Perron Institute for Neurological and Translational Science.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.16/V15

Topic: C.03. Parkinson's Disease

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Title: Bicycling suppresses abnormal beta oscillations in the basal ganglia of Parkinson's disease patients, while walking enhances them specifically in patients who freeze

Authors: L. STORZER¹, J. ARENS¹, J. HIRSCHMANN¹, O. ABBASI¹, M. GRATKOWSKI², D. SAUPE², J. VESPER³, M. BUTZ¹, A. SCHNITZLER^{1,3}, *S. S. DALAL⁴

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Abstract: Freezing of Gait is a disabling gait pattern in patients with advanced stages of Parkinson's disease (PD). The ability to ride a bike generally remains surprisingly unaffected in these patients despite severe gait impairment, suggesting functional differences in the motor network. The purpose of this study was to characterize and contrast the oscillatory dynamics underlying bicycling and walking in the basal ganglia and motor cortex.

We present the two first experiments directly comparing bicycling and walking in PD patients with electrodes implanted in the subthalamic nuclei (STN) for deep brain stimulation. 13 PD patients participated in the first study (5 freezers / 8 non-freezers, 10 bilateral / 2 unilateral STN implants). A follow-up study investigated scalp EEG data in 32 patients (19 freezers / 13 non-freezers) and 16 matched healthy controls.

In patients without freezing of gait, both bicycling and walking led to suppression of subthalamic beta power (13-35 Hz), and this suppression was stronger for bicycling. Freezers also showed a comparable pattern; however, it was superimposed with an oscillation of approximately 18 Hz. This was a movement-induced, narrowband power increase evident even outside of freezing episodes. Our follow-up study suggested that this abnormal 18 Hz oscillation was specific to the STN of freezing patients, as no such effect was observed with scalp EEG over motor cortex.

These results indicate that bicycling facilitates overall suppression of beta power. Furthermore, movement in patients susceptible to freezing specifically leads to exaggerated ~18 Hz synchronization within the basal ganglia but not the motor cortex. These results argue against a crucial role of the primary motor cortex in the pathogenesis of Freezing of Gait and supports the notion that Freezing of Gait originates from the basal ganglia. Suppressing abnormal oscillations in the basal ganglia may therefore form a key strategy in developing potential therapies.

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Poster

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Title: The human dopamine beta hydroxylase rs6271 (t>c) polymorphism is associated with Parkinson's disease and altered protein expression/activity

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Abstract: Background: Norepinephrine is thought to be a key player in the development and pathology of Parkinson's disease. Noradrenergic neuron loss in the locus coeruleus has been shown to precede the loss of dopaminergic neurons in the substantia nigra of PD patients. Dopamine-β-Hydroxylase (DβH) is present in the synaptic vesicles of locus coeruleus noradrenergic neurons and converts dopamine to norepinephrine. Previously, we genotyped 106 PD subjects and 78 controls and found a rare DβH polymorphism, Arg549Cys that was significantly enriched in PD subjects. We hypothesized that genetic coding variants in DβH can result in functional modifications of this protein that lead to altered noradrenergic signaling and increased risk for development of PD.

Methods: We examined the function and availability of the DβH protein in patient sera bearing DβH Arg549Cys variant carriers in both the control and PD groups (n=23) as well as 20 wild-type subjects. Protein quantitation was examined by ELISA analysis and DβH enzyme activity was measured by monitoring the conversion of tyramine to octopamine.

Key Results: We found that this rare allele produces 25% of circulating DβH in patients heterozygous for rs6271, when compared to individuals that were homozygous for the wild-type allele. In both cohorts, the heterozygous subjects displayed higher circulating enzyme activity in spite of lower protein (PD Het. to PD WT: p<0.05, control HET to control WT: p<0.05). However, the heterozygous control group had higher activity than the heterozygous PD group (p=0.03)

Conclusions and Inferences: A single coding region polymorphism in DβH (rs6271) was

significantly over-represented in PD patients and reduces circulating levels of the enzyme. We examined the function and availability of the protein in the sera of both PD and controls patients bearing D β H Arg549Cys. Both control and PD patients, bearing the heterozygote allele had statistically lower D β H protein while the intrinsic enzyme activity was higher. These findings warrant further investigation with in situ models for cellular localization and activity measurements that are more sensitive for D β H in serum. This SNP may be useful as a potential biomarker to assess risk for PD and supports the important role that noradrenergic tone may have in PD.

Disclosures: E. Gonzalez-Lopez: None. K.E. Vrana: None. X. Huang: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS088679
NSF NRT Fellowship DGE-4731815

Title: Abnormal muscle tone during REM sleep is associated with increased rigidity in people with early Parkinson's disease

Authors: *M. E. LINN-EVANS¹, M. N. PETRUCCI², S. L. AMUNDSEN HUFFMASTER², P. J. TUIE², M. J. HOWELL², C. D. MACKINNON²

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Abstract: Parkinson's disease (PD) is commonly associated with REM Sleep Behavior Disorder (RBD), a parasomnia characterized by abnormally elevated muscle tone during REM sleep, termed REM sleep without atonia (RSWA), and dream enactment. We hypothesized that degeneration of systems that regulate muscle tone during REM sleep may also manifest during wakefulness in people with early PD. Rigidity is a cardinal motor symptom of PD defined as increased resistance to passive movement due to elevated muscle tone. Rigidity can be enhanced when passive movement testing is accompanied by voluntary movement of the contralateral limb, known as an activation maneuver. We tested the hypotheses that participants with PD and RSWA (PD-RSWA+) would exhibit higher levels of rigidity and a greater increase in rigidity with an activation maneuver than those with PD without RSWA (PD-RSWA-) and matched controls. Fifty-two subjects participated in the study (17 controls, 16 PD-RSWA-, 19 PD-RSWA+). Participants with PD were tested off medication. Rigidity was quantified using a robotic manipulandum that measured resistive torque while passively moving the subject's

forearm through pronation-supination. Rigidity was measured from the right and left arms, both with and without an activation maneuver (tapping the opposite hand). The slope of the integrated torque was used as a rigidity score. Mixed ANOVAs (factors: group, side, activation) were used to test the hypotheses. Results showed significant main effects of group ($p=0.023$), side ($p=0.019$) and activation ($p=0.018$) and interactions between group x activation ($p=0.041$) and side x activation ($p=0.028$). Post hoc analyses showed rigidity was significantly higher in the PD-RSWA+ group compared to controls ($p=0.021$) and PD-RSWA- ($p=0.015$). The PD-RSWA- group had a larger change in rigidity with activation compared to controls ($p=0.013$) but not compared to the PD-RSWA+ group ($p=0.085$). Rigidity scores were higher and had a larger change with activation on the right side for all groups ($p=0.025$). Our findings demonstrate that RSWA is associated with differences in the expression of rigidity in people with early PD. Consistent with our primary hypothesis, individuals with PD and RSWA had higher rigidity scores than healthy adults and PD subjects without RSWA, suggesting a relationship between muscle tone regulation during sleep and wakefulness. We also found that the PD-RSWA- group showed a larger change in rigidity with activation than controls, but this was not seen in the PD-RSWA+ group. Right side rigidity scores were higher and showed a greater change with activation suggesting that hemispheric dominance may play a role in rigidity.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

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Program #/Poster #: 051.19/W2

Topic: C.03. Parkinson's Disease

Support: GRAMMY Museum

Title: The role of inflammatory cytokines in motor symptoms of Parkinson's disease

Authors: *K. DIAZ-SANTANA, E. L. STEGEMÖLLER, M. KOHUT
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Abstract: Parkinson Disease (PD) is the second most common neurodegenerative disorder worldwide. Many motor symptoms such as bradykinesia, hypokinesia, dysphagia and tremor impact quality of life and are not fully ameliorated by current pharmacological and surgical treatments. This may be due, in part, to the lack of a full understanding of the pathophysiology underlying these symptoms. Previous research has suggested that inflammation may play a significant role in PD, but there is limited research exploring how inflammation directly relates to motor symptoms in PD. The purpose of this study was to explore the associations between

inflammatory cytokines expression levels and motor symptoms in persons with PD. The motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) was completed and scored by a trained rater blind to the study. A blood sample was also collected and monocytes isolated. Through Multiplex assay, a series of blood biomarkers, both pro-inflammatory and anti-inflammatory cytokines, were investigated. Five markers, TGF- α , IL-10, IL-1RA, IL-1 β and TNF- α were selected as inflammatory cytokines of interest. A Spearman correlation was completed to examine the association between the expression levels of the inflammatory cytokines and motor UPDRS scores. UPDRS scores for speech, bradykinesia, tremor, and gait/postural instability were also obtained and entered into the analysis to determine if specific motor symptoms were associated with inflammatory cytokine levels. Results revealed no significant association between levels of inflammatory cytokines and the total motor UPDRS. However, associations were revealed for specific motor symptoms. IL-1 β was significantly correlated to both tremor ($r = 1.00, p = .001$) and upper extremity bradykinesia ($r = -.872, p = .054$). While no significance was revealed, IL-10 and TGF- α were moderately correlated to symptoms of tremor (IL-10: $r = .600, p = .285$; TGF- α : $r = .700, p = .188$). No significant associations were revealed for speech, gait/postural instability and lower extremity bradykinesia. Finally, further analyses revealed no significant correlation between IL-10, TGF- α and IL-1 β expression levels and age. Thus, these results are likely attributed to PD and not aging. Overall, these results are consistent with a growing body of literature that implicates inflammatory cytokines in the progression of PD, and further suggests that inflammatory cytokines, or lack thereof, may be involved in the production and/or progression of select motor symptoms of PD.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.20/W3

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation

Title: Detection of inflammasome proteins in plasma obtained from Parkinson's disease patients

Authors: *F. ANDERSON¹, A. ANDREW¹, K. VON HERRMANN², A. YOUNG³, S. LEE³, M. C. HAVRDA⁴

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Abstract: Parkinson's disease (PD) is a highly prevalent neurodegenerative disease affecting approximately 5 million people worldwide. Neuroinflammation is a widely recognized aspect of PD; however, the impact of inflammation on PD incidence and progression remains unclear. Exposure to environmental toxicants, including pesticides, heavy metals, and industrial solvents has been implicated in PD risk, but the molecular basis and involvement of neuroinflammation is not completely characterized. Inflammasomes, such as NLRP3, are pro-inflammatory intracellular pattern recognition receptors capable of responding to sterile environmental triggers by initiating inflammation and a subcategory of programmed cell death called pyroptosis. Our lab has previously shown that *Nlrp3*^{-/-} mice are resistant to the development of PD symptomatology resulting from exposure to the pesticide and mitochondrial toxin rotenone. More recently we observed expression of NLRP3 in the dopaminergic (DA) neurons remaining in late-stage PD patients. PD is typically diagnosed after the onset of motor impairment, by which time the majority of DA neurons have been lost. Our lab has developed an electrochemiluminescence-based immunosorbent assay for the detection of NLRP3 based on the recognition that inflammasome components are released from activated and distressed cells during the process of pyroptosis. Utilizing this method, we have compared NLRP3 protein levels in human plasma samples collected from PD patients to aged-matched controls. Additionally, we have optimized detection of the downstream NLRP3 targets Caspase 1 and IL-18, suggesting that we may be able to monitor the activity of inflammasomes in plasma. To complement these biochemical studies we have collected surveys from PD patients and controls detailing potentially inflammatory lifestyle factors, occupational exposures, and medical history information to identify environmental risk factors associated with circulating inflammasome components. Our study will allow us to correlate levels of inflammasome activity with environmental exposure data to elucidate their relationship to PD diagnosis. Early diagnosis of PD by detecting related pathologies like neuroinflammation before drastic DA neuron loss has occurred could improve outcomes, as preventative therapies could be employed to slow down disease progression.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Program #/Poster #: 051.21/W4

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation
personal savings of CR Freed

Title: Phenylbutyrate may stop progression of idiopathic Parkinson's disease

Authors: *C. R. FREED¹, S. M. GARCIA¹, G. LEHMICKE¹, M. A. LEEHEY², W. ZHOU¹
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Abstract: There is no drug therapy that can stop the progression of Parkinson's disease. In 2003, Bonifati and colleagues discovered that mutations in the DJ-1 gene cause familial Parkinson's. We took that observation and searched for drugs that could increase expression of DJ-1. We found that the short chain fatty acids butyrate and phenylbutyrate can upregulate the DJ-1 gene and protein in cultures of N27 dopamine neurons and protect those cells from hydrogen peroxide and misfolded proteins. In mice expressing a mutant human form of alpha-synuclein (Y39C) under control of the Thy1 promoter, both butyrate and phenylbutyrate increase expression of DJ-1 protein in the brain and protect the animals from age-related motor and cognitive decline by stopping the aggregation of alpha-synuclein in neurons. The mechanism by which DJ-1 prevents protein aggregation is by increasing lysosome and exosome activity, thereby promoting transfer of alpha-synuclein from neurons into the bloodstream where the protein is eliminated. In mice, phenylbutyrate nearly doubled plasma alpha-synuclein concentrations compared to non-treated control animals. We have given the liquid formulation of the drug, glycerol phenylbutyrate, to 20 subjects with Parkinson's disease and to 20 age-matched controls. As in the mice, glycerol phenylbutyrate increased plasma alpha-synuclein from 50 to 150 per cent of baseline values indicating that the drug improved clearance of alpha-synuclein from neurons into blood plasma. Because phenylbutyrate is a relatively expensive FDA approved drug, we are evaluating the short chain fatty acid butyrate as a potential alternative for human therapeutic use. The successful treatment of transgenic mouse models of Parkinson's disease with butyrate and phenylbutyrate combined with human data that show phenylbutyrate can increase clearance of alpha-synuclein has provided the rationale for double-blind, placebo controlled trials of butyrate and phenylbutyrate to stop progression of Parkinson's disease in humans.

Disclosures: C.R. Freed: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Share in patent for glycerol phenylbutyrate to treat Parkinson's disease. S.M. Garcia: None. G. Lehmicke: None. M.A. Leehey: None. W. Zhou: None.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

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Program #/Poster #: 051.22/W5

Topic: C.03. Parkinson's Disease

Title: SN hyperechogenicity as seen in transcranial sonography (TCS) is a reliable biomarker for disease progression from Stage I to Stage II in early onset Parkinson's disease (EOPD)

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Abstract: Early Onset Parkinson's Disease (EOPD) is characterized by disease onset between ages 41-60, higher risk for treatment related complications, and the need for close monitoring for disease progression. Substantia nigra (SN) hyperechogenicity measured by Transcranial Sonography (TCS) is an established biomarker to differentiate PD from other forms of parkinsonism. We tested the hypothesis that SN hyperechogenicity can be used as a biomarker for disease progression from stage I (unilateral parkinsonism) to stage II (bilateral parkinsonism) in EOPD patients. A total of 22 EOPD patients, did not have genetic forms of PD, and were in Stage I as determined by the Unified Parkinson's Disease Rating Scale (UPDRS) in the "off" state consented into this prospective long-term study. TCS was performed and evaluated by a blinded rater using a Siemens Acuson Sequoia Ultrasound system. Planimetric measurements of SN hyperechogenicity $>0.2 \text{ cm}^2$ were classified as significant on each side. Patients were seen for baseline evaluations (V1), returned for visit 2 (V2) 1 year later, visit 3 (V3) 1.5 years post V1, visit 4 (V4) 2 years post V1, etc. At V1, hyperechogenicity that met $>0.2 \text{ cm}^2$ area was only found on the contralateral SN (N=22) in all but one patient. Side specific UPDRS on the unaffected side was 0 in all subjects at V1, including the one patient with bilateral SN hyperechogenicity $>0.2 \text{ cm}^2$. At V1 mean contralateral and ipsilateral SN hyperechogenicity was $0.267 \pm 0.046 \text{ cm}^2$ and $0.091 \pm 0.079 \text{ cm}^2$ respectively. By V2, 48% of the patients displayed hyperechogenicity above the 0.2 cm^2 threshold ipsilaterally. By V4, the mean ipsilateral SN hyperechogenicity was measured to be $0.294 \pm 0.062 \text{ cm}^2$. A previous report from this study showed all the patients had developed bilateral SN hyperechogenicity by day 750 from V01 whereas only 8 of the 21 subjects had clinically progressed to stage II. This study has continued to follow these subjects further though clinical stage II diagnosis. SN hyperechogenicity of all subjects remains bilateral $>0.2 \text{ cm}^2$ area, an additional 4 subjects have progressed into stage II clinically, leaving 9 of the original cohort still in clinical stage I. In all patients, ipsilateral SN hyperechogenicity gradually increased in area to exceed the 0.2 cm^2 threshold prior to developing stage II disease on UPDRS part III testing in the "practically defined off state" performed by a rater blinded to the TCS results. Our findings confirm the usefulness of SN hyperechogenicity as a biomarker for EOPD progression from stage I to stage II and the difficulties associated with clinical detection of bilateral symptoms in optimally treated EOPD patients despite overnight drug washout.

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Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

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Program #/Poster #: 051.23/W6

Topic: C.03. Parkinson's Disease

Support: 23andMe Collaboration with The Michael J. Fox Foundation

Title: The Parkinson's phenome: Traits associated with Parkinson's disease in a large and deeply phenotyped cohort

Authors: ***K. HEILBRON**¹, A. J. NOYCE², P. FONTANILLAS³, B. ALIPANAHI³, M. NALLS⁴, P. CANNON³

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Abstract: Observational studies have begun to characterize the wide spectrum of phenotypes associated with Parkinson's disease (PD), but recruiting large numbers of PD cases and assaying a diversity of phenotypes has often been difficult. Here, we set out to systematically describe the PD phenome using a cross-sectional case-control design in a large database. We analyzed the association between PD and 840 phenotypes derived from online surveys. For each phenotype, we ran a logistic regression using an average of 5,141 PD cases and 65,459 age- and sex-matched controls. We selected uncorrelated phenotypes, determined statistical significance after correcting for multiple testing, and systematically assessed the novelty of each significant association. We tested whether significant phenotypes were also associated with disease duration in PD cases. PD diagnosis was associated with 149 independent phenotypes. We replicated 32 known associations and discovered 49 associations that have not previously been reported. We found that migraine, obsessive-compulsive disorder, seasonal allergies, and anemia were associated with PD, but were not significantly associated with PD duration, and tend to occur decades before the average age of diagnosis for PD. Further work is needed to determine whether these phenotypes are PD risk factors or whether they share common disease mechanisms. We used a systematic approach in a single large dataset to assess the spectrum of traits that were associated with PD. Some of these traits may be risk factors for PD, features of the pre-diagnostic phase of disease, or manifestations of PD pathology. The model outputs from all 840 logistic regressions are available to the research community and may be used to generate hypotheses regarding PD etiology.

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royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 23andMe. **B. Alipanahi:** A. Employment/Salary (full or part-time);; 23andMe. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 23andMe. **M. Nalls:** A. Employment/Salary (full or part-time);; National Institutes of Health. **P. Cannon:** A. Employment/Salary (full or part-time);; 23andMe. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 23andMe.

Poster

051. Parkinson's Disease: Human Studies: Genetics and Diagnostic

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 051.24/W7

Topic: C.03. Parkinson's Disease

Title: Parkinson's disease and bacteriophages as its overlooked contributors

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Abstract: Background: Bacterial viruses (phages) are also known as primary regulators of gut microbiota stability. We have recently shown that phages may be implicated as being previously overlooked in the development of multifactorial diseases, including those associated with increased intestinal permeability and protein misfolding. The objective of this study was to evaluate the particularities of gut bacteriophages of patients with Parkinson's disease (PD) and their interplay with the bacteria, and to reveal hallmark alterations in bacteriophage composition that may contribute to PD. **Methods:** To explore bacterial and bacteriophage community compositions associated with PD, we used shotgun metagenomics sequencing data of fecal microbiome from 31 patients with PD and 28 controls. Gut microbiota composition was analyzed with MethaPLan and Vipie tools. **Results:** There were numerous alterations in phage contents in PD patients that reshaped microbiota of PD patients, in a manner that might have a functional role in disease onset and progression. Notably, we observed a more than 10-fold decrease in *Lactococcus* spp. abundance in patients with PD compared to controls, due to the increased abundance of strictly virulent phages from the c2-like and 936-like groups. These phages are most frequently isolated from dairy-containing products. Our data indicate that depletion of *Lactococcus* spp. in patients with PD can be explained by the appearance of these environmental lytic phages. In turn, *Lactococcus* bacteria play a significant role in the gut-microbiota axis, being an important source of microbiota-derived neurochemicals such as dopamine and having a particular influence on ENS, which plays an important part in PD. *Lactococci* are also known as

important regulators of gut permeability, alterations in which are also implicated in PD pathogenesis. **Conclusions:** This is the first study to suggest a link between bacteriophages and PD. (1) Bacteriophages caused a depletion of several gut microbiome species in the PD patients compared to the control group. The most pronounced change was a 10-fold decrease in *Lactococcus*. Reduction of *Lactococcus* is particularly relevant, as they are known to be a source of microbiota-derived neurochemicals including dopamine and reductions in prevalence are associated with increased gut permeability. (2) Unlike the control group, patients with PD had elevated levels of strictly virulent, lytic *Lactococcus* phages that caused a significant shift in the relative abundance of *Lactococcus* bacteria. (3) *Lactococcus* phages altered the microbiota of patients leading to functional shifts that may be implicated in the pathogenesis of PD.

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Poster

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Topic: C.03. Parkinson's Disease

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Title: Characterizing the NLRP3 inflammasome in Parkinson's disease

Authors: *M. C. HAVRDA, E. M. MARTINEZ, K. M. VON HERRMANN, F. L. ANDERSON
Geisel Sch. of Med. at Dartmouth, Lebanon, NH

Abstract: Characterizing the molecular basis of neuroinflammation is expected to improve our understanding of the incidence and progression of Parkinson's disease (PD) and other neurologic disorders. Inflammasomes are intracellular pro-inflammatory pattern recognition receptors capable of initiating and propagating inflammation in response to pathogens as well as non-pathogenic cellular damage and stress. These cytosolic complexes are well-characterized in the innate immune system and more recently have been identified as mediators of inflammation in the central nervous system. In PD, sterile cellular stress can manifest in several ways including metabolic and oxidative stress, accumulation and prion-like propagation of misfolded proteins, and the elaboration of toxic DA metabolites and pigment granules. Based on the potential that PD-associated pathophysiology could produce multiple sterile triggers, inflammasomes are compelling candidates for mediating PD-associated neuroinflammation. Our laboratory has characterized the NLRP3 inflammasome in animal models and PD patients. Long-term intragastric exposure to the PD-associated pesticide and mitochondrial toxin rotenone resulted in

Nlrp3-dependent systemic and neurologic inflammation and *Nlrp3*^{-/-} mice were protected from rotenone-induced nigral cell loss. In MPTP treated animals, we observed increased sparing of nigral neurons in *Nlrp3*^{-/-} mice, a dramatic reduction in nigral microgliosis, and suppression of peripheral inflammation. In PD patients, histologic studies revealed elevated *NLRP3* expression in mesencephalic tissues and analysis of exome sequencing data for genetic variation of *NLRP3* identified the rs7525979 variant as associated with a significantly reduced risk of developing PD. Based on the concept that inflammasome proteins are released from distressed cells during the process of pyroptosis, we developed a novel immunoassay and examined NLRP3 protein in plasma identifying a subset of PD patients with significantly elevated circulating NLRP3. Taken together these data improve our understanding of *NLRP3* in PD, suggest that NLRP3 has a key role in PD-associated neuroinflammation, and indicate that targeting inflammasomes may be a reasonable neuroprotective strategy for PD and related disorders.

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Poster

052. Neuromuscular Diseases: Motor Neuron Disease: In Vitro Studies

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Topic: C.06. Neuromuscular Diseases

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SENSHIN Medical Research Foundation
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Title: The proline-arginine repeat protein linked to C9ORF72-ALS/FTD inhibits RNA helicase-mediated ribosome biogenesis and causes neuronal cell death

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Abstract: A GGGGCC repeat expansion in the *C9ORF72* gene has been identified as the most common genetic cause of amyotrophic lateral sclerosis and frontotemporal dementia. The repeat expansion undergoes unconventional translation to produce dipeptide repeat proteins. Although it has been reported that dipeptide repeat proteins cause neurotoxicity, the underlying mechanism has not been fully elucidated. In this study, using an *in vitro* cell-based assay, we first show that the enforced expression of proline-arginine repeat protein (poly-PR) causes neuronal cell death.

We also show that the expression of poly-PR reduces levels of ribosomal RNA and that the poly-PR-induced neuronal cell death is restored by the acceleration of ribosome biogenesis. This result suggests that the poly-PR-induced inhibition of ribosome biogenesis contributes to the poly-PR-induced neurotoxicity. Furthermore, we show that poly-PR interacts with multiple DEAD-box RNA helicases and inhibits the function of at least one of them, and that the reduction in the levels of some RNA helicases results in both the decrease in ribosomal RNA levels and the increase in neuronal cell death. Altogether, these results suggest that poly-PR causes neuronal toxicity by inhibiting the DEAD-box RNA helicase-mediated ribosome biogenesis.

Disclosures: **H. Suzuki:** None. **M. Matsuoka:** None.

Poster

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Topic: C.06. Neuromuscular Diseases

Support: Strategic International Collaborative Research Program (SICORP) from AMED

Title: ADAR2-mediated RNA editing of extracellular linear and circular RNAs: A potential biomarker of amyotrophic lateral sclerosis

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Abstract: There are no reliable biomarkers of amyotrophic lateral sclerosis (ALS). In the vast majority of sporadic ALS, RNA editing at the glutamine/arginine site of GluA2 mRNA is abnormally reduced in the motor neurons due to downregulation of adenosine deaminase acting on RNA 2 (ADAR2) (Kawahara et al, Nature 2004; Hideyama et al, Neurobiol Dis 2012). Conditional ADAR2 knockout mice exhibit ALS-like phenotype, including progressive motor dysfunction resulting from loss of motor neurons and TDP-43 pathology-like TDP-43 mislocalization in the ADAR2-lacking motor neurons (Hideyama et al, J Neurosci 2010; Yamashita et al, Nat Commun 2012). These lines of evidence suggest a pivotal role of ADAR2 downregulation in the ALS pathogenesis. Extracellular RNAs including mRNA and circular RNA (circRNA) attract researcher's attention as potential biomarkers of human diseases including neurodegenerative diseases. To address whether ADAR2-dependent RNA editing sites of these extracellular RNAs may reflect intracellular ADAR2 activity, we searched for adenosine-to-inosine (A-to-I) sites by comparing the conditional ADAR2 knockout mice and

wild-type mice. After scrutinizing the human RNAs analogous to mouse RNAs with A-to-I sites, we found 28 candidate A-to-I sites in human RNAs. Then, we investigated for ADAR2-dependency of these sites in the host RNAs expressed in human-derived cultured cells and their culture medium by overexpression or knockdown of ADAR2. We found five RNAs that had ten ADAR2-dependent A-to-I sites, including a novel ADAR2 site, in SH-SY5Y cells and their culture medium. Furthermore, we demonstrated circRNA that has an ADAR2-dependent A-to-I site in the SH-SY5Y cells and their culture medium. The present results indicate that changes in the editing efficiencies at these A-to-I sites of host extracellular RNAs reflect cellular ADAR2 activity, suggesting that changes in the editing efficiencies at the A-to-I sites of these RNAs in the body fluids would be potential biomarkers of sporadic ALS. Support: Strategic International Collaborative Research Program (SICORP) from AMED.

Disclosures: **T. Yamashita:** None. **N. Hirose:** None. **S. Teramoto:** None. **A. Tamaoka:** None. **S. Kwak:** None.

Poster

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ALSFAC

Title: Distinct molecular mechanisms contribute to nuclear pore complex alterations in C9orf72 ALS/FTD

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Abstract: The motor neuron disease Amyotrophic Lateral Sclerosis (ALS) and the second most common form of early-onset dementia, Frontotemporal Dementia (FTD), comprise a spectrum of fatal neurodegenerative diseases. An intronic GGGGCC hexanucleotide repeat expansion (HRE) in the C9orf72 gene is the most common cause of familial ALS and FTD. Together, both toxic RNA and DPRs are thought to contribute to a gain of toxicity mechanism in disease.

Nucleocytoplasmic transport, a key process in maintaining cellular function occurring through the nuclear pore complex, has recently emerged as a prominent pathomechanism underlying C9orf72 mediated toxicity. However, the precise mechanisms underlying disruptions in nucleocytoplasmic transport, the organization and structure of nuclear pore complexes, and pathologic alterations induced by pathologic repeat RNA and DPR proteins remain largely unknown. Recently, we have shown that stress granule (SG) assembly can impair nucleocytoplasmic transport via the recruitment of specific nucleoporins to SGs in HEK293 cells thus linking the two most prominent pathomechanisms of ALS. We now seek to understand the precise mechanisms by which the C9orf72 HRE leads to impaired nucleocytoplasmic transport in ALS/FTD. Given the intricate role of the nuclear pore complex in regulating nucleocytoplasmic transport, we have used super resolution SIM microscopy to investigate the distribution of key nuclear pore proteins (nucleoporins) in nuclei isolated from control and C9orf72 iPSC derived neurons. We assessed 10-16 nucleoporins spanning each domain of the nuclear pore complex in 5 control and 5 C9orf72 iPSC lines and found that C9orf72 nuclei lack expression of specific nucleoporins. Furthermore, we have defined distinct subsets of nucleoporins: 1. Those whose expression is altered; 2. Those that localize to SG in iPSC derived motor neurons, and 3. Those that appear to aggregate in a *SG independent* manner. Mechanistically, cyclohexamide pulse chase experiments suggest that turnover of specific nucleoporins may be altered in C9orf72 iPSC derived neurons, potentially implicating changes in the annulate lamelli, the ER zone required for nuclear pore complex assembly. In addition, treatment of iPSC derived neurons with inhibitors of SG assembly mitigates deficits specifically in those nucleoporins which localize to SG. In contrast, reduction of pathologic C9orf72 repeat RNA and DPRs mitigates all observed alterations in the nuclear pore complex. Together, these data suggest that the C9orf72 HRE elicits multiple cellular responses contributing to alterations in the nuclear pore complex in ALS/FTD.

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Poster

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Topic: C.06. Neuromuscular Diseases

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Title: miRNAs shuttled by exosomes derived from mesenchymal stem cells move spinal cord astrocytes isolated from SOD1^{G93A} mice at the late phase of disease from a neurotoxic to a neuroprotective phenotype

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal non-cell autonomous neurodegenerative disease characterized motoneuron (MN) death. Indeed, ALS involves in MN damage also microglia and astrocytes, which promote an inflammatory environment that contributes to MN degeneration. In particular, astrocytes acquire a reactive phenotype able to secrete neurotoxic cytokines. In a previous study we observed that intravenous administration of bone marrow-derived mesenchymal stem cells (MSCs) in SOD1^{G93A} mice, an animal model of human ALS, prolongs survival probability, ameliorates motor skills and reduces gliosis and inflammation in spinal cord (PMID: 22481270). These beneficial effects were determined by MSC-produced paracrine factors. We have speculated that MSCs exert their action at least in part through the transfer to target cells of miRNA shuttled by their released exosomes. To understand the mechanisms underlying the effects of MSCs, we studied here the activity of MSC-derived exosomes and exosome-shuttled miRNAs on cultured astrocytes prepared from spinal cord of late symptomatic SOD1^{G93A} mice and verified whether exosomes and their miRNAs could modulate astrocyte activation and reduce the inflammatory environment surrounding MNs. We observed a significant increase of GFAP and vimentin, markers of astrocytic reactive phenotype, in SOD1^{G93A} compared to WT astrocytes. After treatment with exosomes, the expression of GFAP and vimentin was reduced by 40% and 80%, respectively. We also analyzed the expression of a number of pro- and anti-inflammatory cytokines. The level of IL1 β , TNF α , IL6 was significantly higher in SOD1^{G93A} astrocytes. The same as above, exposure of SOD1^{G93A} astrocytes to exosomes resulted in a significant decrease of these cytokines expression, by 65%, 80% and 60%, respectively. We also detected a significant decrease of the expression of IL-10, an anti-inflammatory cytokine, in SOD1^{G93A} astrocytes and a reversal to normal levels upon exposure to exosomes. The expression of NLRP3, a protein involved in neuroinflammation-induced necroptosis, was increased in SOD1^{G93A} compared to WT astrocytes and this increase was reversed (70%) by treatment with exosomes. To further understand the exosome mode of action, we transfected SOD1^{G93A} astrocytes with miR-466q and miR-467f, which are up-regulated in MSCs and in their derived exosomes. Both miRNAs decreased IL1 β and TNF α hyper expression detected in SOD1^{G93A} astrocytes. Thus, exosomes and their miRNAs ameliorate the inflammatory state and promote a shift of astrocytes to a neuroprotective phenotype. These data are promising for translational pre-clinical trials in SOD1^{G93A} mice.

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Poster

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS072735

Title: Homocysteine sensitizes the mouse neuromuscular junction to oxidative stress via nitric oxide

Authors: J. S. WANG, *C. A. LINDGREN
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Abstract: Homocysteine, a redox-active metabolite of the methionine cycle, is of particular clinical interest due to its association with various neurodegenerative diseases including Amyotrophic Lateral Sclerosis. It has been previously established that homocysteine exacerbates ROS-induced damage to motor neurons. To assess the role of homocysteine at the mammalian neuromuscular junction, neurotransmission was monitored via electrophysiology at the mouse Epitrochleoanconeus (ETA) muscle. Preparations were pre-incubated in homocysteine prior to inducing ROS and recordings were taken before and after ROS treatment. In this study, homocysteine was observed to sensitize the neuromuscular junction to ROS-induced depression of spontaneous transmission frequency, an effect we found to be mediated via an NMDA Receptor and Nitric Oxide. Application of the NMDA receptor antagonist DL-2-Amino-5-phosphonopentanoic acid returned transmission to baseline levels. Disrupting nitric oxide activity with either the NOS I antagonist N^ω-Nitro-L-Arginine methyl ester hydrochloride or the NO scavenger 2-(4-Carboxyphenyl)-4,4,5,5-tetramethyl-imidazoline-1-oxyl-3-oxide potassium salt returned transmission to baseline levels. Moreover, replacing homocysteine with the exogenous NO donor Diethylamine NONOate diethylammonium was sufficient to reconstitute homocysteine-induced effects at the neuromuscular junction. Interestingly, a novel secondary effect was observed where homocysteine itself depresses quantal content, an effect found to be mediated by NMDARs independently of nitric oxide and ROS. Collectively, these data present a novel model of two distinct pathways through which homocysteine affects neurotransmission at the neuromuscular junction. Characterizing homocysteine's mechanism of action is of particular clinical relevance as many treatments for ALS are centered around mitigating homocysteine-induced pathologies.

Disclosures: J.S. Wang: None. C.A. Lindgren: None.

Poster

052. Neuromuscular Diseases: Motor Neuron Disease: In Vitro Studies

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Program #/Poster #: 052.06/W14

Topic: C.06. Neuromuscular Diseases

Title: Disease relevant *in vitro* assays for amyotrophic lateral sclerosis in motor neurons derived from control and patient iPSCs

Authors: *S. JAIN¹, M. BSIBSI¹, M. JANUS¹, J. DE GROOT¹, D. F. FISCHER²

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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that progressively and irreversibly affects motor movement due to the death of motor neurons in the brain and spinal cord. About 90% of ALS cases have no known etiology while the remaining 10% have a genetic cause. Mutations in over 20 genes have been associated with familial ALS with mutations in 4 genes accounting for the majority of familial cases - SOD1, FUS, TDP-43 and C9orf72.

Charles River has established cultures of human induced pluripotent stem cells from two control and four ALS patients, with each patient cell line harboring a mutation in one of the 4 genes which account for the majority of familial ALS. We have also optimized and implemented a robust motor neuron differentiation protocol that is amenable to high throughput screening. Using this protocol, the differentiated neurons express mature motor neuron markers, including Islet1 and SMI32 by day 30 of differentiation.

This physiologically relevant cell system allows high throughput screening of small molecule libraries or functional genomics-type approaches (RNAi/ CRISPR-Cas9), using high content imaging or biomarker readouts. Some of the disease relevant readouts that have been developed for screening:

- C9orf72 RNA foci formation
- C9orf72 di-peptide aggregation (RAN translation products)

Additional disease relevant phenotypes in development include:

- Stress granule formation
- Nucleo-cytoplasmic transport
- TDP-43, FUS and SOD1 localization and aggregation

We will present data demonstrating the robustness of our assays in iPSCs derived motor neurons and how, in combination with multi-parametric high content imaging can help the discovery of novel targets and drugs for therapeutic intervention for this disease with high unmet medical need.

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Poster

052. Neuromuscular Diseases: Motor Neuron Disease: In Vitro Studies

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Topic: C.06. Neuromuscular Diseases

Support: DFG KY96/1-1

Cure SMA

Cologne Fortune

SMA Europe

Title: Muscle-secreted CTRP3 regulates ERK and PI3K pathways in motor neurons and NMJ formation in spinal muscular atrophy

Authors: *W. A. REHORST¹, N. BROCKE-AHMADINEJAD³, A. IONSECU⁴, D. WINTER³, S. CIRAK¹, B. WIRTH², E. PERLSON⁴, M. J. KYE¹

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Abstract: Spinal muscular atrophy (SMA) is the second most frequent autosomal recessively inherited neuromuscular disorder causing childhood lethality. While it is primarily considered as a motor neuron disease, it has been shown that other organs and tissues such as skeletal muscle and heart exhibit intrinsic defects. As one of the most recognized characteristics of SMA is the morphological and functional defect of the neuromuscular junction (NMJ) and since skeletal muscle has been acknowledged as an endocrine organ, we investigate whether muscle-secreted molecules play a role in neuronal gene expression and function at the NMJ.

By systemic screening with mass spectrometry combining SILAC and AHA labelling, we profiled secreted proteins from WT and SMA muscle cells. We have identified 894 proteins in the secretome and 2981 proteins in cells, and stringent statistical analysis led to a list of 8 upregulated and 10 downregulated proteins in SMA muscle secretomes. Among them, C1q/tumor necrosis factor-related protein 3 (C1QTNF3, also known as CTRP3) is the most significantly downregulated protein in SMA muscle secretomes. We further confirmed that CTRP3 expression and secretion is indeed reduced in *Smn*-depleted C2C12 cells. Moreover, CTRP3 levels were reduced in craniofacial and distal limb muscle tissue of an SMA mouse model. Intensive evaluation of the downstream pathways of CTRP3 in motor neurons showed that it positively regulates ERK and PI3K pathways. Currently, we are testing the function of CTRP3 for NMJ formation and maintenance using microfluidic chambers.

The contribution of secreted molecules from diseased muscles to motor neuron physiology in neuromuscular disorders is poorly understood. Here, we report an interesting molecule differentially secreted from SMA muscle cells, and regulating gene expression in motor neurons. This study will help us to uncover the unappreciated mechanisms contributing to NMJ impairment in SMA.

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Poster

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Program #/Poster #: 052.08/W16

Topic: C.06. Neuromuscular Diseases

Title: Role of PACAP/EGFR/MMP-2 axis in an *in vitro* model of amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by selective loss of motor neurons in the CNS. Approximately 20% of ALS cases are associated to mutations in the Cu/Zn-superoxide dismutase-1 (SOD1) gene (Rosen et al., 1993). We have recently characterized the transcriptional profiles of motor cortex samples from sporadic ALS (SALS) patients and differentiated these into two subgroups (SALS1 and SALS2), based on differentially expressed genes, encoding for 70 potential therapeutic targets (Aronica et al., 2015; Morello and Cavallaro 2015). Through a meta-analysis approach, we have identified three target genes commonly upregulated both in SOD1G93A transgenic mice and SALS2 motor cortex, including pituitary adenylate cyclase-activating polypeptide (PACAP), epidermal growth factor receptor (EGFR) and matrix metalloproteinase 2 (MMP-2). Considering that a functional association between PACAP and EGFR in lung cancer cells has been already described (Moody et al., 2011), here we investigated whether a similar PACAP/EGFR/MMP-2 axis deregulation is involved in the pathophysiology of ALS.

This study has been performed in a motor neuronal cell line of mouse NSC-34, stably transfected for the inducible expression of low quantities of wild or mutant SOD1G93A. Our results have shown that treatment with 100 nm PACAP is able to rescue cells degeneration following growth factors deprivation, as previously demonstrated in a iPSC-derived model of ALS (Bonaventura et al., 2017). Conversely, cells viability is drastically decreased following treatment with PAC1

antagonist PACAP(6-38) or EGFR tyrosine kinase inhibitor gefitinib. We found that PACAP addition increased EGFR tyrosine phosphorylation through protein kinase A, but not phospholipase C. Moreover, peptide addition triggered the activation of survival signal MEK/ERK pathway, and increased the expression of MMP-2, whose levels are drastically reduced after serum starvation.

Our findings suggest that a deeply characterization of the mechanism linking PACAP/EGFR/MMP-2 axis to SOD1 mutation may open a new perspective for ALS therapy.

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Poster

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Topic: C.06. Neuromuscular Diseases

Support: ALS Canada- Brain Canada Discovery Grant

Title: A 3D tissue-engineered spinal cord model to recapitulate the amyotrophic lateral sclerosis phenotype

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Abstract: Background: Amyotrophic lateral sclerosis (ALS) is an incurable and life-threatening neurodegenerative disease that affects 2 to 5 of every 100 000 adults. ALS causes death of motor neurons (MN), mainly located in the spinal cord. Therefore, the movement information transmitted by MN to muscles is disturbed. ALS also triggers patient death due to respiratory failure within 3 to 5 years of diagnosis. A mutation in the Superoxide Dismutase 1 (SOD1) gene has been identified as a cause of ALS in some patients, inducing protein misfolding and aggregation in MN. MN, astrocytes, microglia, myoblasts and Schwann cells constitute a metabolic unit and it has been shown that non-neuronal cells could contribute to the ALS development. **Objectives:** Our purpose is to extract MN, astrocytes, microglia, myoblasts and Schwann cells from mice reproducing the disease phenotype, to maintain these cells in long term culture and to develop a 3D spinal cord model reproducing ALS. **Methods:** MN have been extracted from transgenic spinal cord mouse embryos and astrocytes, microglia, myoblasts and Schwann cells from adult mice (after disease onset) overexpressing the mutant (SOD1G93A) or normal (SOD1WT) human SOD1 protein. These cells have been characterized by immunofluorescence, purified by gradient density separation, and co-cultured on 3D collagen

sponges. **Results:** The 3D model showed the close cell-cell interaction between astrocytes and MN. We also noticed that when SOD1G93A MN were cultured in the 3D model, in presence of mutant astrocytes, mutant microglia or both, there was a reduction in TUJ1-positive neurites, and these latest were less branched, compared to controls made of SOD1WT astrocytes and microglia. MN are able to organize into nerve fibers in presence of normal or diseased glial cells, but axonal migration was found 25% shorter with ALS glial cells. **Conclusion:** MN are able to organize into nerve fibers in presence of normal or diseased glial cells, but axonal migration is affected by ALS glial cells. The main advantages of the 3D model are to allow the combination of all cell types (MN, astrocytes, microglia, Schwann cells and myoblasts) in the same tissue, to make any healthy and diseased cell combination, to explore the process of axonal migration in 3D and to perform long-term culture (over 2 months). In vitro ALS modeling should provide a better understanding of the disease mechanism, and could serve as a screening platform for future drugs.

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Poster

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Topic: C.06. Neuromuscular Diseases

Support: Above and Beyond, LLC

Title: The M1311V variant of the copper transporter ATP7A is associated with impaired trafficking and copper homeostasis in models of motor neuron disease

Authors: *R. P. BOWSER¹, A. STARR¹, N. BAKKAR¹, Z. T. MCEACHIN², I. LORENZINI¹, M. CHAUNG³, R. KRAFT³, D. C. ZARNESCU³, G. J. BASSELL², E. HUTCHINS⁴, R. REIMAN⁵, K. VAN KEUREN-JENSEN⁵, N. ZAHLER⁶, S. ALWORTH⁸, J. ICHIDA⁹, P. R. AUGUST⁷, A. BÉTOURNÉ¹⁰, N. M. BOULIS¹¹, R. SATTLER¹

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Abstract: Disrupted copper distribution causes neurodevelopmental and neurodegenerative diseases, such as Wilson's disease and Menkes disease, and is proposed to contribute to the pathogenesis of Alzheimer's disease and Parkinson's disease. Due to its role in mitochondrial function, antioxidant activity, and synaptic transmission, changes in copper homeostasis can

cause a broad range of cognitive and motor deficits. Different mutations in the P-type ATPase copper transporter ATP7A are known to cause distinct diseases including Menkes, occipital horn syndrome, and a distal motor neuropathy. We recently identified a variant of ATP7A in a patient diagnosed with amyotrophic lateral sclerosis (ALS), a fatal disease defined by the degeneration of upper and lower motor neurons. The M1311V substitution is associated with reduced localization of ATP7A at the trans-Golgi membrane at basal copper levels in patient-derived fibroblasts and induced pluripotent stem cells differentiated into motor neurons (iPSC-MNs), as well as in HeLa cells overexpressing the mutation. In addition, reduced redistribution of ATP7A-M1311V to the cellular membrane in response to increased extracellular copper is observed in these models. Quantitative analysis of copper homeostasis reveals significant functional deficits in ATP7A-M1311V patient fibroblasts, and decreased dendritic complexity and aberrant spontaneous firing in patient iPSC-MNs further suggest impaired neuronal functions. Alterations in gene expression have also been examined via RNA sequencing of patient fibroblasts and iPSC-MNs. Expression of the ATP7A-M1311V variant in *Drosophila* motor neurons results in motor deficits, as measured by larval turning assays. Ongoing studies include therapeutic drug screens using dendritic complexity and survival assays in ATP7A-M1311V patient iPSC-MNs and characterization of CRISPR/Cas9-corrected patient iPSC-MNs. Together, these observations suggest that the M1311V variant of ATP7A negatively impacts its role as a copper transporter and impairs several aspects of motor neuron morphology and function across multiple models.

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Poster

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Topic: C.06. Neuromuscular Diseases

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HI18C0158

Title: Functional characterization of ALS-iPSC-derived neurons upon various cellular stresses

Authors: Y.-K. LEE¹, P. JEON¹, H.-E. CHOI¹, B.-K. KAANG², *J.-A. LEE¹

¹Hannam Univ., Dajeon, Korea, Republic of; ²Sch. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Mutations in fused in sarcoma (FUS), or TAR-DNA binding protein 43(TDP-43), are associated with familial amyotrophic lateral sclerosis (fALS) and some forms of frontotemporal lobar dementia (FTLD). However, little is known about how specific ALS-causing mutations induce neurodegeneration in patient-derived neurons under various cellular stresses. Therefore, in this study, to understand cellular pathogenesis in ALS patient-derived neurons with physiological relevance, we have generated induced pluripotent-stem cell (iPSC) from ALS patient-derived fibroblasts with genetic mutation in TDP43 (A382T), or FUS (H517Q) using nonviral method. We validated pluripotency of each iPSC line (TDP43(A382T), FUS(H517Q), control ND) in vitro and in vivo. Many ALS-linked mutants are associated with stress granules and protein inclusions. To investigate how endogenous ALS mutant protein could affect cellular toxicity, each iPSC was differentiated into neurons and we examined their cellular toxicity and protein quality control pathway such as autophagy, or UPS upon various cellular stresses. We will present functional characterization of ALS- iPSC-derived neurons. Our study will provide cellular pathogenic mechanism of ALS associated with FUS/TDP43 mutation upon cellular stresses and therapeutic insight regarding ALS cellular pathology

Disclosures: Y. Lee: None. P. Jeon: None. H. Choi: None. B. Kaang: None. J. Lee: None.

Poster

052. Neuromuscular Diseases: Motor Neuron Disease: In Vitro Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 052.12/X2

Topic: C.06. Neuromuscular Diseases

Support: Cure SMA
SMA Europe

Title: Restoring disturbed energy homeostasis in spinal muscular atrophy

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Abstract: Spinal muscular atrophy (SMA) is a neuromuscular disease, characterized by loss of lower alpha motor neurons, which leads to proximal muscle weakness. The majority of SMA is caused by loss or mutation of the ubiquitously expressed gene, Survival of Motor Neuron 1 (*SMN1*). Various molecular mechanisms contributing to the SMA patho-phenotype have been described, among them metabolic defects and especially dysfunctional mitochondria have been reported. The main source of neuronal energy is glucose and motor neurons depend on mitochondrial oxidative phosphorylation (OxPhos) to cover their high energy demands. SMA motor neurons show hyperexcitability which requires even higher energy levels. Recent findings show that neurons can adapt to increased energy demands by activating mitochondrial biogenesis

or the mobilization of glucose transporter to the plasma membrane for enhanced fuel supply. The translocation of glucose transporters to the axonal plasma membrane triggered by activity of the synapses is directed by activity of the adenosine monophosphate activated protein kinase (AMPK).

Motor neurons from a SMA mouse model show signs of disturbed energy homeostasis such as a reduced number of functional mitochondria along the axon and lower basal ATP concentration compared to control motor neurons. ATP levels are reduced by 56% in SMA motor neurons compared to control ones. Furthermore, AMPK is activated in SMA motor neurons due to the decreased energy level. We want to restore ATP levels as well as disturbed energy homeostasis by improving mitochondrial function or glycolysis in SMA motor neurons.

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Poster

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Topic: C.06. Neuromuscular Diseases

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CONICYT 21151563 (PM)

Title: Skeletal myotubes expressing human SOD1(G93A) trigger motor neuron neurodegeneration through the release of a toxic factor(s)

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Abstract: Despite that ALS is considered a central nervous system disease, considerable studies indicate that restricted expression of hSOD1^{G93A} in mouse muscles induces motor neuron degeneration and ALS symptomatology. To gain insights into the mechanisms underlying motor neuron neurodegeneration, we established an *in vitro* model system using rodent hSOD1^{G93A} myotubes and wild-type motoneurons. Muscle conditional media (MCM) was prepared from cultured primary myotubes from neonatal mice expressing human SOD1^{G93A}. Non-transgenic

MCM-mSOD1^{WT} was used as controls. Wild-type primary rat ventral spinal cord cultures (VSCN) (8-10% motor neurons) were incubated at 4 DIV with MCMs. For each sample we tested motor neurons survival (SMI32/MAP2 immunostaining), ROS production (measured with DCF probe) and c-Abl phosphorylation. MCM-hSOD1^{G93A} robustly reduced motoneuron survival (40%) in 7 DIV VSCN cultures. Strong ROS production and c-Abl phosphorylation were observed after MCM-hSOD1^{G93A} application. We further used a compartmentalized microfluidic system to expose motor neurons to MCMs both distally (myotubes compartment) and proximally (motor neurons somas compartment). We evaluated mitochondrial trafficking speed through axons and calcium events in motor neurons somas, as possible mechanisms of molecular pathology. Our data provide evidence that skeletal myotubes expressing an ALS-causing gene leads to motoneuron pathology and neurodegeneration through a non-autonomous mechanism.

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Poster

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Program #/Poster #: 052.14/X4

Topic: C.06. Neuromuscular Diseases

Support: Advancing a Healthier Wisconsin
John & Phoebe Lewis Stem Cell Research Program
Quadracci Memorial Fellowship

Title: Characterization of iPSC-derived motor neurons from monozygotic twins discordant for ALS

Authors: *E. R. SEMINARY¹, L. WHEELER², M. MEJAKI², D. FEE², P. BARKHAUS², A. D. EBERT¹

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Abstract: Amyotrophic lateral sclerosis (ALS) is an adult onset neurodegenerative disorder characterized by the loss of the motor neurons of the brain and spinal cord. While a small subset of cases can be linked to a specific mutation, the majority of incidences are due to unknown causes. This lack of known mutations has made studying sporadic ALS (sALS) difficult due to the inability to generate cell culture and animal models. However, the development of induced pluripotent stem cells (iPSCs) has made modeling sALS more feasible, as these cells can be generated from any patient regardless of genetic background. Yet, without isogenic controls,

differentiating between the contribution of genetic susceptibility and environmental factors to the disease phenotype can be challenging. In this study, we were presented with the relatively rare opportunity to generate iPSCs from 61 year old monozygotic twins that are discordant for ALS and with no known family history. The affected twin was diagnosed at age 59, while the healthy twin was asymptomatic at the time of sampling. Peripheral blood was collected from the affected and healthy twin during a routine clinic visit. Peripheral blood mononuclear cells were immediately isolated from whole blood samples and reprogrammed using sendai virus expressing Oct4, Sox2, Klf4, and c-myc. Multiple iPSC clones were generated and two clones from each patient were used for further analysis. The selected clones expressed the pluripotency markers Oct4, Sox2, and Tra1-81 at similar levels by immunocytochemistry (ICC). Undifferentiated colonies generated embryoid bodies and differentiated into the three germ layers expressing SMA, AFP, and Tuj1 by ICC. We then differentiated the iPSCs to ventral spinal cord motor neurons showing no difference in differentiation efficiency or viability based on islet1 and ChAT immunofluorescence. There is also no overt morphological difference between the motor neurons from the affected and healthy twins. We are currently focusing attention on protein aggregation and the function of the protein quality control system as we have previously observed increased insoluble SOD1, TDP-43, and optineurin in conjunction with impaired activation of protein chaperones in mutant SOD1, TDP-43, and C9orf72 ALS iPSC-derived motor neurons. Additionally, we are performing whole genome sequencing in an effort to identify the presence of known and/or novel disease-causing variants in the affected twin compared to the unaffected twin. iPSCs offer a window into disease processes for seemingly sporadic conditions, and these discordant monozygotic twin iPSC lines will be a valuable tool to better understand ALS disease pathology.

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Poster

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Topic: C.06. Neuromuscular Diseases

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Title: Dipeptide repeat oligomers in ALS and FTD

Authors: *N. N. BHATT¹, M. CARRETERO-MURILLO¹, S. A. MCALLEN¹, A. ELLSWORTH¹, U. SENGUPTA¹, J. RUDRA², R. KAYED¹

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Abstract: The hexanucleotide repeat expansion in *C9orf72* is one of the most common causes of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The hexanucleotide expansion is a structural polymorphism formed by a GGGGCC repeat region that impedes traditional transcription, and leads to several error-prone transcripts. These transcripts can undergo non-AUG dependent translations, producing several dipeptide repeat-containing proteins (DPRs) including GP, GA, GR, PA and PR. The DPRs form toxic neuronal inclusions in patients with ALS and FTD as suggested by several studies. Some dipeptide repeats such as GA, aggregate as well as sequester other cellular proteins. Given increasing evidence that soluble species, like oligomers, are the main cause of neurotoxicity in neurodegenerative conditions such as Alzheimer's and Parkinson's disease, here we investigated the ability of DPRs to aggregate and form toxic oligomers. We synthesized dipeptides (GA, PR, and GR) of varying repeat lengths and used biophysical as well as biochemical assays to characterize the aggregates *in vitro*. The results suggest the propensity for DPR, specially GR and PR to form oligomeric structures which are capable of self-seeding and cross-seeding with other disease associated proteins such as tau. We also tested the toxicity of the varying DPR aggregates alone and in combination with tau protein *in vivo*. Moreover, we investigated the presence of DPR oligomers in ALS and FTD human samples and their potential role in disease pathogenesis. Thus, the ability to detect and characterize oligomeric DPR has great potential to further the understanding of these diseases and aid in the development of targeted therapeutics.

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Poster

052. Neuromuscular Diseases: Motor Neuron Disease: In Vitro Studies

Location: SDCC Halls B-H

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Program #/Poster #: 052.16/X6

Topic: C.06. Neuromuscular Diseases

Title: Phenotypic functional *in vitro* screening of patient iPSC-derived motor neurons used for *in vitro* HTS disease modeling with AI-based analysis of micro electrode array data

Authors: *B. M. BADER¹, M. SEGURA CASTELL¹, K. JUEGELT¹, M. L. HENDRICKSON², L. SCHULTZ¹, O. H.-U. SCHROEDER¹

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Abstract: Patient-derived iPSC models have been designed for various indications promising higher physiological relevance and thus, better translation to the *in vivo* situation. Their application eventually may decrease attrition rates in drug discovery and development. We focused on investigating motor neuron diseases (MND) such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), both causing loss of motor neurons and associated

symptoms. Here, we phenotypically describe the consequence of the genetic variation present in ALS and SMA patient iPSC-derived motor neurons on the functional activity and network connectivity. We further elucidated how functional ALS and SMA phenotypes separated from controls during network establishment to enable compound testing to rescue the disease phenotypes. We cultured patient iPSC-derived motor neurons (BrainXell) and controls on multiwell micro-electrode arrays (MEA, Axion Biosystems) for several weeks to analyze their functional network activity patterns by multi-parametric analysis (NeuroProof). Our results showed reproducible spontaneously active motor neuron networks with synchronized activity. We identified disease-specific functional phenotypes and showed how reference compounds can affect them. In conclusion, we show that hiPSC-derived motor neurons are able to produce functional in vitro phenotypes which can be associated with known motor neuron diseases. By using artificial intelligence-based multivariate MEA data analyses combined with reproducible physiologically relevant iPSC neuron models we provide a functional phenotypic assay platform for high throughput compound screening.

Disclosures: **B.M. Bader:** A. Employment/Salary (full or part-time);; NeuroProof GmbH. **M. Segura Castell:** A. Employment/Salary (full or part-time);; NeuroProof GmbH. **K. Juegelt:** A. Employment/Salary (full or part-time);; NeuroProof GmbH. **M.L. Hendrickson:** A. Employment/Salary (full or part-time);; BrainXell. **L. Schultz:** A. Employment/Salary (full or part-time);; NeuroProof GmbH. **O.H. Schroeder:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroProof GmbH.

Poster

052. Neuromuscular Diseases: Motor Neuron Disease: In Vitro Studies

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Title: Enhanced CSF NF-L levels and deranged neurofilaments: Conjoined players of motor neuron degeneration in sporadic ALS

Authors: *V. K¹, A. M. VARGHESE², S. SHRUTHI², A. NALINI³, P. A. ALLADI², T. N. SATHYAPRABHA², T. R. RAJU²

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Abstract: INTRODUCTION: Neurofilament (NF) pathology is suggested to be the most prominent cause of motor neuron death in Amyotrophic Lateral Sclerosis (ALS). Primary abnormalities in either expression or phosphorylation of NF can directly lead to motor neuron injury through formation of the aggregates. **AIM:** To examine the NF-L levels in CSF of ALS patients (ALS-CSF) and investigate the cytoskeletal abnormalities in a cellular model of sporadic ALS. **METHODS:** NF-L levels in ALS-CSF (n=60), nonALS-CSF (NALS-CSF; n=10) and normal CSF (N-CSF; n=13) were measured using ELISA. NSC-34 cells were exposed to ALS-CSF (10% v/v for 48hrs) and subsequently immunocytochemistry and Western blotting of NF-H, NF-L and SMI-33 (antibody against phosphorylated and non-phosphorylated NF-H & NF-M) were performed to localize and semi-quantitate the expression of NF. Ultrastructural changes were investigated by electron microscopy. **RESULTS:** NF-L level in ALS-CSF was up-regulated by nearly 7 and 4 folds when compared to NALS and normal CSF respectively. Exposure of NSC-34 cells to ALS-CSF resulted in up-regulation of SMI-33 and the NF-L subunit, whereas NF-H level remained unaltered. SMI-33 immunolabeling under normal conditions displayed a filamentous network that exhibited the evenly distributed cytoskeletal architecture of NSC-34 cells. However in the cells exposed to ALS-CSF, cytoplasmic aggregates and beaded neurites were prominently seen. This corroborated with the deranged appearance of neurofilaments ultrastructurally. **CONCLUSION:** Our study demonstrates altered expression and accumulation of neurofilament subunits in the soma and processes of ALS-CSF exposed NSC-34 cells. These observations parallel our earlier finding of the presence of aggregated phosphorylated neurofilaments, pointing towards defective axonal transport. Indicative of this, we have previously demonstrated that neurofilament aggregates sequester vital cellular proteins such as choline acetyl transferase in ALS-CSF exposed NSC-34 cells. Amongst the three subunits, NF-L deserves closer scrutiny since, alongside its role in proper assembly of neurofilaments, it acts as a sink for reactive nitrating species which are prominently increased in ALS. Furthermore, its significantly enhanced levels in CSF confer it a supplemental biomarker status for sporadic ALS.

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Poster

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Topic: C.06. Neuromuscular Diseases

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Title: Retromer complex deficiency in amyotrophic lateral sclerosis astrocytes may induce motor neuron degeneration

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Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease that results in the death of motor neurons (MNs) in the spinal cord and brain. While ALS is usually sporadic (sALS), transgenic (Tg) mice expressing mutant genes associated with the familial form effectively model the disease. One such model expresses a G93A mutation in SOD1 (SOD1^{G93A}). Mounting evidence both in vivo and in vitro has shown that astrocytes play an integral role in this neurodegeneration, likely in part due to protein trafficking and processing defects which result in non-cell-autonomous MN degeneration. Here, we study the possible contribution of the retromer complex to these defects. The retromer complex takes part in a recycling pathway that traffics proteins away from the endosome to the trans-Golgi network and to the plasma membrane. This complex has a well-studied role in protein trafficking—particularly that of APP in neurons—, and defects in the retromer have been linked to multiple neurodegenerative diseases. Here, we show a marked decrease of retromer core components—Vps35, Vps26a, and Vps29—in cultured astrocytes from SOD1^{G93A}-Tg mice. We show that this difference is not due to overexpression of the SOD1 protein, as wild-type overexpressing astrocytes do not show the same decrease in expression. Furthermore, we see that spinal cord extracts from SOD1^{G93A}-Tg mice also express lower levels of all three core components. Finally, astrocytes cultured post-mortem from patients afflicted with sALS also express lower levels of the core components, further linking retromer deficiency with ALS pathology. Here, we investigate the nature and effects of such deficiency, including differences in the stability of the complex, differences in the rate of degradation of the core components, downstream deficiencies in protein processing, and effects on motor neuron viability. We thus explore our hypothesis that decreased function of the retromer complex may contribute to aberrant protein processing in astrocytes, which may, in turn, contribute to ALS neurodegeneration.

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Poster

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Topic: C.06. Neuromuscular Diseases

Title: Role of m⁶A RNA methylation in motor neuron function

Authors: *G. NTERMENTZAKI¹, D. BONANOMI², J. H. HANNA³, F. LOTTI¹

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Abstract: N⁶-methyladenosine (m⁶A) is a highly pervasive modification in the RNA that regulates its splicing, translation and stability. Recent advances in studying RNA modifications have revealed that m⁶A exerts a critical role in stem cell self-renewal and differentiation in the mouse nervous system. However, the role of m⁶A in the adult mammalian nervous system under physiological and pathological conditions remains largely unexplored. A recent study revealed that components of the m⁶A machinery play an important role in axon regeneration in the peripheral nervous system following nerve injury in mice. In the present study, we aim at determining the role of m⁶A RNA modification in motor neuron function under normal conditions as well as in neurodegeneration. By depleting different determinants of the m⁶A pathway in embryonic stem cell-derived motor neurons we identified the components of the m⁶A machinery that are important for motor neuron survival and neurite outgrowth. We are currently combining RNA immunoprecipitation with transcriptome-wide analysis of gene expression and splicing changes upon depletion of these factors to identify the downstream targets mediating these phenotypes. We anticipate that the identified targets will have far-reaching implications for our understanding not only of motor neuron function, but also of the molecular mechanisms of neurodegeneration as well as to design informed therapeutic approaches for these devastating disorders.

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Poster

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Title: The AR N/C interaction in SBMA- molecular mechanisms and therapeutic potential

Authors: *A. LISBERG¹, R. CADILLA², P. EIDAM², D. MERRY¹

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Abstract: Spinal and bulbar muscular atrophy (SBMA) is a neurodegenerative disease caused by a CAG trinucleotide repeat expansion within the androgen receptor (AR) gene, which leads to misfolding and aggregation of the translated AR protein. The mutation leads to motor neuron degeneration and muscle atrophy in affected individuals. Studies from our lab have shown that an interdomain interaction of the AR called the N/C interaction is required for its toxicity. However, the mechanistic basis for this role is unknown. To better understand the role of the AR N/C interaction in SBMA we first investigated the effect of the repeat expansion on the N/C interaction using mammalian two-hybrid analysis and proximity ligation assays. We hypothesized that repeat expansion might increase the strength or duration of this interaction. Surprisingly, we observed that mutant AR exhibits a somewhat reduced N/C interaction compared to wild-type AR. In order to investigate potential mechanisms mediating the neuroprotective effect of blocking the N/C interaction, we investigated its effect on nuclear export. Recent studies from our group (see poster by Arnold et al.) reveal defective nuclear export of the polyglutamine expanded AR. We observed that the F23A mutation does not significantly increase nuclear export of AR in a heterokaryon shuttling assay, indicating that the state of AR in the nucleus that is influenced by the N/C interaction is important for AR toxicity. The demonstrated role of the AR N/C interaction in SBMA models suggests that blocking the interaction may represent a potential therapeutic target. A promising new class of selective androgen receptor modulators (SARMs) are characterized by their ability to block the AR N/C interaction while promoting AR transcriptional activity. In this study, we screened a set of SARMs for their therapeutic potential in SBMA. As expected, nearly all of the SARMs screened blocked the DHT-induced N/C interaction. Moreover, several SARMs showed anti-AR aggregation effects in SBMA cell models. Continued studies will reveal the therapeutic potential of targeting the AR N/C interaction in SBMA.

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Poster

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Title: Investigating the effects of ALS-associated mutant KIF5A on primary neurons

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Abstract: The neurodegenerative disease Amyotrophic Lateral Sclerosis (ALS) is a fatal motor neuron disease of unknown etiology that is currently without a cure. Our lab, amongst others, recently discovered that the kinesin family member 5A gene (KIF5A) is associated with ALS. Examination of the mechanism by which mutant KIF5A leads to ALS can provide insight into the role transport plays in the pathogenesis of ALS, not just ALS caused by mutations in KIF5A. The first objective of our work was to identify a mutant specific phenotype in cultured primary neurons caused by the expression of ALS-associated mutant KIF5A. The second objective was to establish a system to screen this phenotype. The rationale for this work is that in the future, screens will be performed on the effects of various small molecules on the mutant specific phenotype. The results of the screens can provide valuable insight into what cellular pathways are affected by mutant KIF5A, providing potential therapeutic targets for ALS. To reach our objectives, we transfected primary cortical neurons with either WT or mutant KIF5A and monitored their survival over time. We were able to detect a significant decrease in the survival of neurons expressing ALS-associated mutant KIF5A when compared to those expressing WT KIF5A. We then proceeded to optimize procedures so that a high throughput screen can be performed to examine survival of KIF5A mutant expressing neurons treated with small molecules. By the conclusion of the optimization, we were able to use robotics to transfect cells in 384 well plates, to add small molecules to these cells, and to image these neurons over time. In addition, we were able to devise an accurate method of automated image analysis to determine the survival of cells. In total, we have established a system which will be used to identify cellular pathways affected by ALS-associated mutant KIF5A and provide insight into the mechanisms which lead to ALS.

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Poster

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Program #/Poster #: 052.22/X12

Topic: C.06. Neuromuscular Diseases

Title: Preclinical pharmacodynamic muscle markers of ALS progression

Authors: *G. SRUBEK TOMASSY¹, Y. LIU², M. ZHANG¹, L. SUN³, Y. LUO¹, C. ROBERTS², A. R. MCCAMPBELL¹

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Abstract: ALS is a neuromuscular disease where progressive loss of neuromuscular junctions leads to denervation of skeletal muscles, with consequential muscle wasting, atrophy and paralysis. Despite ongoing efforts aimed at finding meaningful biomarkers of disease diagnosis and progression, current clinical practice still relies mostly on functional scores such as the revised El Escorial and the Awaji. Identifying novel, measurable markers of disease progression and target engagement is crucial for running robust preclinical studies able to reliably support drug development programs. Furthermore, identification of markers translatable to the clinics can provide valuable tools that not only can work as efficacy endpoints but that can also help stratifying the right patients at the right time of disease progression. Using the SOD1-G93A mouse as a genetic model of ALS, we have built a transcriptional profile of a specific muscle in the hind limbs (tibialis anterior, TA) at early time points, from 5 to 9 weeks of age (pre-symptomatic). With this approach, we have identified a series of differentially expressed genes (DEGs) whose expression changes as early as 7 weeks of age, and we have validated some of the most promising candidates through WB and Elisa. By combining these newly identified muscle-specific markers with other established markers of neurodegeneration and neuromuscular function we aim at further improving our ability to run time-effective studies and reach faster and more reliable go/no-go decisions.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.01/X13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Teva Pharmaceutical Industries

NIH grants NS095181

NIH grants NS095279

NIH grants NS101701

Title: Therapeutic effects of laquinimod on Huntington's disease mice

Authors: *P. YIN, X.-J. LI, S. LI

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Abstract: In Huntington's disease (HD), the misfolded huntingtin (htt) protein carries an expanded polyglutamine (polyQ) repeat, forms aggregates in ageing neuronal cell, and causes progressive neurodegeneration and neurological symptoms. Growing evidence indicates that non-neuronal mutant htt toxicity also plays an important role in HD. We reported a HD mouse model (PLP-150Q) that selectively expresses N-terminal mutant Htt (1-208 amino acids) with 150Q in oligodendrocyte, which could cause age-dependent neuropathology with severe demyelination that affects neuronal function and axonal integrity. Because the demyelination or white-matter abnormality is observed in HD patient's brain at the early or pre-symptomatic stages, finding an early intervention or drug that can delay or prevent demyelination may be an effective therapeutic means for HD. Laquinimod (LAQ) is a novel oral drug that can diffuse freely across the blood-brain barrier. It has been used in clinical trials of multiple sclerosis or an experimental autoimmune encephalomyelitis rat model to prevent severe demyelination. We propose to examine the effect of LAQ on the neurological phenotypes of the PLP-150Q HD mouse model and to test the protective effect against demyelination. Through a battery of behavior tests to assess the therapeutic effects of LAQ, we treated PLP-150Q mice and the control PLP-23Q mice ($n \geq 24$) at the age of 2-4 months with two doses of LAQ (5mg/kg and 25mg/kg) for 1-2 months. The LAQ could improve the behavioral phenotypes, the motor function, and depressive behavior. In addition, using immunohistochemistry, electron microscopy, and biochemistry assays, we found that LAQ could increase myelin basic protein (MBP) expression, and partly restore axon degeneration of PLP-150Q mice. Mechanistic studies revealed that LAQ could increase the mRNA expression levels of myelin genes at the transcriptional level, through reducing the binding of mutant Htt to Myelin regulatory factor (MYRF) and increasing MBP promoter activity. Our findings demonstrate the potential

therapeutic effect of LAQ on Huntington disease mice that express mutant Htt selectively in oligodendrocytes.

Disclosures: X. Li: None. S. Li: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.02/X14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2012M3A9C4048795
NRF-2017R1A5A2014768

Title: MHE182 inhibits lipopolysaccharide-induced neuroinflammation by regulating NF- κ B signaling

Authors: *I. JU, C. KWAK, Y. KWON, M. OH
Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Neuroinflammation occurred in brain is considered as a pathological factor causing neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and multiple sclerosis. Since microglia play a pivotal role in maintaining neuroinflammation, targeting microglia is regarded as an efficient treatment for neurodegenerative diseases. In this study, we investigated anti-neuroinflammatory effects of a herbal medicine which is traditionally used to treat several inflammatory disorders in Korea. We explored inhibitory activities of MHE182, the herbal medicine extract, on lipopolysaccharide (LPS)-stimulated microglia *in vitro* and *in vivo*. We found that MHE182 suppresses microglial activation by blocking nuclear factor kappa B (NF- κ B) signaling and thereby inhibiting downstream pro-inflammatory factors — tumor necrosis factor- α , interleukin-1 β , cyclooxygenase-2, inducible nitric oxide synthase, prostaglandin E2 and nitric oxide in BV2 microglial cells. Also, we confirmed the inhibitory effects of MHE182 on neuroinflammation in mouse brains by measuring the number of ionized calcium-binding adapter molecule 1-positive cells that indicates microglial activation, in cortex and hippocampus. These results suggest that MHE182 could inhibit neuroinflammation mediated by activated microglia and may be an effective regulator of inflammatory disorders in brain. This study was supported by Bio-Synergy Research Project (National Research Foundation (NRF)-2012M3A9C4048795) of the Ministry of Science, ICT, and Future Planning (MSIP) through the NRF. This study was also supported by Medical Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2017R1A5A2014768).

Disclosures: I. Ju: None. C. Kwak: None. Y. Kwon: None. M. Oh: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.03/Y1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH CounterACT Grant # 5U01NS058162-07

Title: Comparing the antiseizure and neuroprotective efficacy of LY293558, diazepam, caramiphen, and LY293558-caramiphen combination against soman in a rat model relevant to the pediatric population

Authors: *J. P. APLAND¹, V. ARONIADOU-ANDERJASKA², T. H. FIGUEIREDO³, V. I. PIDOPLICHKO², K. ROSSETTI⁴, M. F. M. BRAGA²

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Abstract: The currently FDA-approved anticonvulsant for the treatment of status epilepticus (SE) induced by nerve agents is the benzodiazepine diazepam. However, diazepam does not appear to offer neuroprotective benefits. This is particularly concerning with respect to the protection of children, because in the developing brain, synaptic transmission mediated via GABA_A receptors, the target of diazepam, is still weak. In the present study, we exposed 21-day-old male rats to 1.2xLD₅₀ soman, and compared the antiseizure, anti-lethality, and neuroprotective efficacy of diazepam (10 mg/kg), LY293558 (an AMPA/GluK1 receptor antagonist; 15 mg/kg), caramiphen (an antimuscarinic with NMDA receptor-antagonistic properties; 50 mg/kg), and LY293558 (15 mg/kg)+caramiphen (50 mg/kg), administered 1 h post-exposure. Diazepam, LY293558, and LY293558+caramiphen, but not caramiphen alone, terminated SE, with the LY293558+caramiphen treatment acting significantly faster, and produced survival rate greater than 85%. Thirty days after soman exposure, neurodegeneration in limbic regions was most severe in the caramiphen-treated group, minimal to severe—depending on the region—in the diazepam group, absent to moderate in the LY293558-treated group, and totally absent in the LY293558+caramiphen group. Amygdala and hippocampal atrophy, severe reduction of spontaneous inhibitory activity in the basolateral amygdala, and increased anxiety-like behavior in the open field and acoustic startle response tests were present in the diazepam and caramiphen groups, while the LY293558 and LY293558+caramiphen groups did not differ from controls. The combined administration of LY293558 and caramiphen, by blocking mainly AMPA, GluK1, and NMDA receptors, is a very effective anticonvulsant and neuroprotective therapy against soman in young rats. The experimental protocol was approved by the Animal

Care and Use Committee at the USAMRICD and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government.

Disclosures: J.P. Apland: None. V. Aroniadou-Anderjaska: None. T.H. Figueiredo: None. V.I. Pidoplichko: None. K. Rossetti: None. M.F.M. Braga: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.04/Y2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MCPHS University Faculty Grant 2017-18

Title: Evaluation of the neuroprotective potential and mechanism of action of a dithiolethione compound against manganese-induced toxicity in SH-SY5Y neuroblastoma cells

Authors: *S. BETHARIA, K. GUGNANI, C. YOO
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Abstract: Manganese (Mn) is an essential mineral at low concentrations, but is considered neurotoxic at higher concentrations. Upon environmental or occupational exposure, Mn accumulates in the basal ganglia and increases the level of oxidative stress. The resulting damage to dopaminergic and GABAergic neurons is expressed as manganism, a condition involving symptoms of motor and cognitive slowing similar to those observed in Parkinson's disease (PD). Dithiolethiones are sulfur-containing heterocyclic molecules naturally found in cruciferous vegetables. The simplest member of this class, 3H-1, 2-dithiole-3-thione (D3T) has been shown to exert neuroprotective effects in *in vitro* models of PD. By activating the nuclear factor erythroid derived 2-related factor 2 (Nrf2) pathway, D3T causes the induction of various enzymes including glutamate-cysteine ligase catalytic subunit (GCLC), which catalyzes the rate-limiting step in the synthesis of the endogenous antioxidant glutathione (GSH). Hence D3T is known to enhance the cells' natural capacity to fight oxidative insult in established models of PD. Given that Mn is a neurotoxicant known to also increase oxidative stress, we evaluated if the neuroprotective effect of D3T observed in PD extended to *in vitro* models of Mn toxicity. SH-SY5Y neuroblastoma cells were exposed to either manganese chloride (MnCl₂) alone (1 - 800 μM), or pre-incubated with D3T (6.25 - 100 μM) followed by exposure to MnCl₂. A cell viability assay was performed, which demonstrated that 100 μM D3T provided significant neuroprotection against the toxic effects of up to 500 μM MnCl₂. A similar concentration-

dependent decrease in the levels of reactive oxygen species (ROS) was also observed with D3T pretreatment in Mn-exposed cells, suggesting that the counteraction of Mn-induced oxidative stress was a neuroprotective mechanism utilized by this compound. Increased levels of cellular GSH measured using a luminescence-based kit; and increased expression of Nrf2 and GCLC proteins measured using the Western blot technique in D3T pretreated cells will help establish a detailed pathway for these observed neuroprotective effects against Mn-induced toxicity. All experiments were conducted in triplicates, and data was analyzed using ANOVA followed by a *post hoc* test.

Disclosures: S. Betharia: None. K. Gugnani: None. C. Yoo: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.05/Y3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CAPES (SLC)

FAPESB (SLC)

MS Society (AMB)

BBSRC (AMB)

Title: Neuroprotective, anti-neuroinflammatory and myelinogenic effects of agathisflavone in *in vitro* and *ex vivo* models of neuroinflammation and demyelination

Authors: *M. A. CARNEIRO^{1,3}, F. PIEROPAN², N. DOURADO³, A. B. DA SILVA³, R. S. FERREIRA³, V. D. A. DA SILVA³, C. S. SOUZA⁴, A. M. BUTT², S. L. COSTA³

¹Sch. of Pharm. and Biomed. Sci., ²Univ. of Portsmouth, Portsmouth, United Kingdom; ³Univ. Federal of Bahia, Salvador, Brazil; ⁴Univ. of Sheffield, Sheffield, United Kingdom

Abstract: Flavonoids are polyphenolic plant compounds with known anti-inflammatory and cytoprotective properties. Here, we have examined the neuroprotective, myelinogenic and anti-inflammatory potential of agathisflavone (FAB), a flavonoid derived from the Brazilian plant *Poincianella pyramidalis* (Tul.) in *in vitro* and *ex vivo* models of neuroinflammation and demyelination. Neuroinflammation was examined in co-cultures of glial and neural cells derived from the cortex of newborn and embryo Wistar rats that were exposed for 24h to lipopolysaccharide (LPS, 1µg/mL) or IL1β (10ng/mL) and then treated for 24 h with FAB (1µM). FAB exerted a neuroprotective effect against LPS or IL1β-induced damage significantly decreasing the expression of caspase-3 in neurons co-labelled with β-tubulin, as well as reduced the Fluoro-Jade B fluorescence intensity and nitric oxide concentration. FAB also demonstrated anti-inflammatory properties against LPS-induced neuroinflammation, as shown by decrease of

microglial proliferation (IBA1/BrdU) and pro-inflammatory marker (IBA1/CD68), and in the expression of inflammatory molecules CCL5, CCL2, CX3CL11, IL6, prostaglandin and IL18, as determined by qPCR. The effect of FAB on demyelination was examined in *ex vivo* organotypic cerebellar slices from Sox10-EGFP and PLP1-DsRed transgenic mice. Cerebellar slices were maintained for 7 days *in vitro* (DIV) and after that were incubated overnight in 5mg/mL in lysolecithin (LPC) and then treated with FAB 5.0 and 10 μ M for 2 DIV. Compared to control, LPC did not alter the number of SOX10-EGFP or PLP1-DsRed positive cells, but reduced the myelin index and the myelinated axons, as determined by immunostaining for myelin basic protein (MBP) and/or neurofilament. Notably, after treatment with FAB in both concentrations, there was an increase in the myelin index, as well as in the myelinated axons. We also demonstrated that LPC did not reduce the density of Purkinje cells, but altered their morphology and that this effect could be reversed by FAB. Furthermore, LPC induced increase in the number of microglia and in the activation of both M1 and M2 microglia profile, as seen by IHC to IBA1+CD16/32 and IBA1+CD206 respectively. On the other hand, we demonstrated that FAB 5.0 and 10.0 μ M were able to reduce the number of microglia IBA1+ and CD16/32+, but did not alter the expression of CD206. Finally, FAB 5.0 μ M was able to enhance the number of NG2 positive cells. Together these findings provide evidence that FAB has a significant protective effect against neuroinflammation and demyelination in *in vitro* and *ex vivo* models, but more studies are being conducted in order to elucidate its mechanism of action.

Disclosures: M.A. Carneiro: None. F. Pieropan: None. N. Dourado: None. A.B. Da silva: None. R.S. Ferreira: None. V.D.A. Da silva: None. C.S. Souza: None. A.M. Butt: None. S.L. Costa: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.06/Y4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH P20GM103466
Alan M. Krassner Fund

Title: Scaffold based hybrids as new nicotinic acetylcholine receptor ligands

Authors: *D. GUNDISCH, L. KOSTUR, X. WU, A. R. BURGOYNE
Col. of Pharm. UHH, Hilo, HI

Abstract: We used the strategy of combining several pharmacophoric fragments that can modulate nicotinic acetylcholine receptors (nAChRs) and monoamine oxidase B (MAO-B) to produce compounds, so-called hybrids, with potentially higher efficacy for the treatment of

neurodegenerative diseases. Pharmacophore fragments known for strong interaction with their respective targets have been used to create our first generation compound library. Among them are e.g. diazabicyclic systems known to be privileged scaffolds for the interaction with nAChRs and the neuroprotective propargylamine moiety for MAO-B binding. During the chemical synthesis we identified intermediate compounds with desired pharmacophoric elements which have been evaluated in addition. These compounds serve as backup compounds for future libraries. Structure affinity relationship studies for four different nAChR subtypes (α4β2, α7, α3β4, muscle) using radioligand binding assays provided important insights for further profiling strategies. All compounds showed preference for the α4β2 nAChR subtype with K_i values ranging from 16 pM to 800 nM. Selected compounds were evaluated in *in vitro* screening assays for MAO-B using crude mitochondrial fractions from rat brains and first active ligands have been obtained. Current *in silico* docking studies for nAChRs and MAO-B assist in the understanding of the interaction modes of the new compounds and in the design of new hybrids with improved biological activities.

Disclosures: D. Gundisch: None. L. Kostur: None. X. Wu: None. A.R. Burgoyne: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

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Program #/Poster #: 053.07/Y5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AG048918

Title: Sub-chronic administration of metformin selectively protects primate dopamine neurons from methamphetamine-induced damage: Investigations on its mechanism and potential use in Parkinson's disease

Authors: *J. K. BLACKBURN, D. W. CURRY, B. STUTZ, R. H. ROTH, J. D. ELSWORTH
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Abstract: In Parkinson's disease and during normal aging there is a progressive loss of midbrain dopaminergic neurons. The loss of DA innervation to forebrain regions has been firmly linked with declines in motor and cognitive function in aging and PD. Despite knowing that mitochondrial alterations and oxidative stress play key roles in the loss of DA neuron function in aging and PD, there are currently no therapeutic treatments that can preserve the dwindling population of midbrain DA neurons. In the young nonhuman primate (NHP) brain, DA neurons are remarkably resilient to drugs that induce oxidative stress and compromise mitochondrial function (e.g., MPTP, methamphetamine), thus understanding differences in protective mechanisms present in early life could open new avenues for treatment in PD. We have so far

identified two anti-oxidant mitochondrial proteins that are relatively highly expressed early in life: Uncoupling protein-2 (UCP2) and Paraoxonase-2 (PON2). Interestingly, female brains express a higher level of PON2 than males, which corresponds to the lower prevalence of PD in females. Targeting these 'protection factors' is a putative new avenue for PD treatment. Some recent rodent studies have indicated that the anti-diabetic drug, Metformin, protects the brain against loss of dopamine neurons in models of PD. An established target of Metformin is AMP-activated kinase (AMPK), which is an up-stream regulator of UCP2 and peroxisome proliferator-activated receptor gamma coactivator 1- (PGC1), the 'master regulator of mitochondrial biogenesis'. However, metformin activates a range of downstream molecular events and it is not yet clear how it protects dopamine neurons from damage. In our study, we found that sub-chronic metformin treatment of St Kitts green monkeys reduced methamphetamine-induced alteration of dopamine function in selective brain regions, including substantia nigra and prefrontal cortex. As UCP isoforms (UCP 2, 4, 5) and PON2 are possible targets of metformin, we compared their expression in different brain regions and at different ages in NHP brain. In summary, the results further our understanding of the parameters of metformin's neuroprotective actions and help evaluate its possible role as a treatment of PD and some sequelae of aging.

Disclosures: D.W. Curry: None. B. Stutz: None. R.H. Roth: None. J.D. Elsworth: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.08/Y6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: McCrorie-West Family
Alzheimer Society of Manitoba
Canadian Diabetes Association
Alzheimer's Society of Canada
St. Boniface Research Foundation

Title: Secreted amyloid precursor protein alpha activates nf kappa b and increases sod2 expression in cultured peripheral neurons

Authors: *B. AULSTON, G. GLAZNER
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Abstract: Sensory neuropathy is characterized by peripheral nerve degeneration and is a common complication in patients with diabetes. We have found previously that diabetes may contribute to the development of peripheral neuropathy by reducing the activity of the transcription factor NFκB, and in turn, decreasing the expression of neuroprotective genes such

as MnSOD (SOD2), in DRG neurons. MnSOD is a mitochondrial scavenger of ROS and it's hypothesized that insufficient MnSOD antioxidant capacity is a key pathological feature of diabetes and neurodegenerative disorders. Previous reports demonstrate that insulin treatment can reverse MnSOD deficits in diabetic DRG neurons and that MnSOD protects against diabetic peripheral neuropathy. In addition to insulin, the amyloid precursor protein (APP) cleavage product secreted amyloid precursor protein alpha (sAPP α) can induce NF κ B activity and activate insulin signaling pathways and therefore may offer an alternative strategy to increase MnSOD expression and reduce oxidative stress that is associated with diabetic neuropathy. With this in mind, we examined the effect of sAPP α on NF κ B and MnSOD in DRG neurons cultured from healthy and diabetic rats. We found that sAPP α increased neurite outgrowth in both diabetic and wild-type (Wt) DRG neurons and that DRG neurons had a greater response to sAPP α treatment. Furthermore, we determined that sAPP α increased NF κ B activity in diabetic DRG neurons and increased MnSOD expression. In total, these findings suggest that activation of the NF κ B-MnSOD axis may underlie the protective effects of sAPP α on DRG neurons. Moreover, our results indicate that the development of sAPP α based therapies as a treatment for diabetic-induced neuropathy is warranted.

Disclosures: **B. Aulston:** None. **G. Glazner:** None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

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Program #/Poster #: 053.09/Y7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

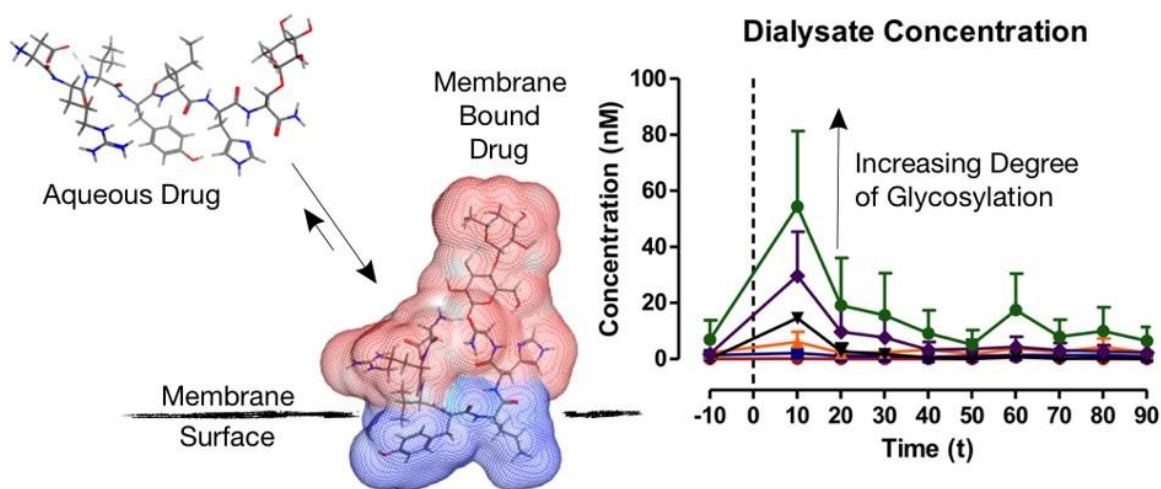
Support: NIH NINDS NS091238
Migraine Research Foundation
Michael J. Fox Foundation

Title: Glycopeptides as systemically delivered CNS active drugs from endogenous peptide hormones

Authors: ***J. M. STREICHER**¹, T. FALK², M. HAY³, C. APOSTOL⁴, M. BARTLETT², M. HEIEN⁴, G. MOLNAR¹, C. LIU⁴, C. SMITH⁴, L. SZABO⁴, R. POLT⁴
¹Pharmacol., ²Pharmacol. and Neurol., ³Evelyn F. McKnight Brain Inst., ⁴Chem. and Biochem., Univ. of Arizona, Tucson, AZ

Abstract: Peptide neurotransmitters related to enkephalins, dynorphins, angiotensin, secretins, and other peptide hormones, both cyclic and linear, have been converted to carbohydrate-bearing O-linked glycopeptide drug candidates. Short glycopeptides (5-7 residues) have been created which produce mu opioid agonism, delta opioid agonism, or synergistic mu + delta opioid

agonism. By linking helical amphipathic “addresses” to these opioid “messages” it was possible to enhance their anti-nociceptive effects *in vivo* in rodents. Glycosylated angiotensin analogues with neuroprotective activity have been synthesized that show extended stability and blood-brain barrier (BBB) penetration in male rats. Large pituitary adenylate cyclase-activating peptide (PACAP) compounds have also been created with longer linear sequences. These have neuroprotective and neurorestorative potential. MS^N analysis in conjunction with microdialysis has been used to measure both stability and BBB penetration of these compounds in male rodents. With this advance it is now possible to determine pharmacokinetic profiles for this new class of drugs that are typically cleared from serum by the kidneys. Using this approach, we demonstrate that glycosylated peptide drugs possess enhanced metabolic stability and BBB penetration. Molecular weight (MW) does not appear to affect BBB penetration rates, at least in the range of MW’s examined so far, 550—3,500 Daltons. This approach thus has great promise to make even large neuropeptides drugable. We hypothesize that this ability to penetrate the BBB is due to the ability of the glycopeptides to adopt conformations that render them either highly water soluble or highly amphipathic structures that associate strongly with biological membranes, e.g. “bioussian behavior.”



Disclosures: **J.M. Streicher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teleport Pharmaceuticals, LLC. **T. Falk:** None. **M. Hay:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ProNeurogen. **C. Apostol:** None. **M. Bartlett:** None. **M. Heien:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teleport Pharmaceuticals, LLC. **G. Molnar:** None. **C. Liu:** None. **C. Smith:** None. **L. Szabo:** None. **R. Polt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teleport Pharmaceuticals, LLC.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.10/Y8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: EGF-induced MAPK-mediated Calpain2 activation triggers a neuroprotective priming mechanism against Oxygen-Glucose deprivation; implication of AMPAR downregulation and degradation of their scaffolding PDZ proteins

Authors: *H. JOURDI¹, F. H. KOBEISSY², A. DAOU³

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Abstract: Calpains are Ca⁺⁺-dependent regulatory proteases that truncate various enzymes, cytoskeletal proteins, neurotransmitter receptors, and ion channels. However, under physiological conditions, Calpain2 (a.k.a. mCalpain) rapid activation depends on MAP Kinase and can be achieved in the presence of BAPTA-AM, an intracellular Ca⁺⁺ chelator (Jourdi et al., 2010). Treatment of primary cortical neuronal cultures (PCNC) with EGF and EGF-like cytokines reduces AMPAR expression and levels of their scaffolding proteins GRIP1 and SAP97 (Yokomaku D et. al., 2005; Namba H et. Al., 2006). Here, we show that EGF treatment in primary neurons and cultured hippocampal slices causes the appearance of lower molecular weight bands representing calpain-mediated SAP97 and GRIP1 degradation products. The appearance of these degradation products is sensitive to calpain, MAPK and ErbB1 (a.k.a. EGF receptor) inhibition. EGF and related cytokines are neuroprotective against various neurotoxic conditions, including ischemia. Neuroprotection against ischemia can also be achieved by brief exposure of nervous tissues to ischemic conditions (ischemic preconditioning or priming). Thus, can EGF pretreatment exert neuroprotective priming-like effects against oxygen-glucose deprivation (OGD)? Indeed, EGF pretreatment followed by OGD does not cause additional accumulation of SBDP or SAP97 and GRIP1 degradation products, implying abrogated calpain activation during OGD. Equally important are the findings that calpain inhibition eliminates the neuroprotective effects of EGF pretreatment against OGD. The interaction of EGF pretreatment with calpain activation is also assessed in the context of a priming-like effect of EGF against OGD using acute hippocampal slices taken from mice lacking or over-expressing the endogenous calpain inhibitor, calpastatin. The data indicate that calpastatin expression levels in mutant mice are inversely correlated with calpain activation and SAP97 and GRIP1 degradation under OGD conditions, confirming the neuroprotective role for calpastatin. In conclusion, EGF-triggered calpain activation leads to down-regulation of AMPARs and degradation of their scaffolding PDZ proteins. Our results imply that EGF-induced AMPAR downregulation

contributes to EGF's neuroprotection against OGD injury. These findings may have important implications for stroke and ischemia.

Disclosures: H. Jourdi: None. F.H. Kobeissy: None. A. Daou: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.11/Y9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Exploring the effects of irradiation and dietary polyphenol supplementation on behavior and neurogenesis in mice

Authors: *A. D. TROFIMOVA¹, N. KALYNOVSKA¹, D. Y. XU², H. CAO³, M. S. DULCICH¹, N. M. BAJWA¹, D. BAYLINK², R. E. HARTMAN¹

¹Psychology, ²Sch. of Med., ³Hematology and Oncology, Loma Linda Univ., Loma Linda, CA

Abstract: The health benefits of dietary polyphenols have been established across many disease states. For example, studies from our laboratory have previously demonstrated their effectiveness in mouse models of Alzheimer's disease and irradiation, as well as humans with cardiovascular issues. Exposure to radiation, such as that which may be experienced by astronauts on a deep space mission, has been associated with observable behavioral deficits, decreased neurogenesis, and reduced spleen weight in rodents. In the current study, C57bl/6 mice received dilute pomegranate juice for 10-16 days prior to birth (via maternal drinking water intake) and for 13-14 weeks after birth (via their own drinking water). The mice were then irradiated with a single 2 Gy dose of proton radiation at a rate of ~1.5 Gy min, followed by behavioral testing. From 4-6 days later, the mice received BrdU injections, followed by sacrifice at 1 week after irradiation. Their brains were removed, sliced with a cryostat, and stained with DAPI, Ki-67, BrdU, and doublecortin to examine proliferation of new cells in the dentate gyrus and subventricular zones. Spleens were also removed and weighed. We hypothesized that proton irradiation would induce behavioral disturbances, reduce cell proliferation in the brain, and reduce spleen weight, and that exposure to dietary polyphenols would ameliorate those effects. Neither irradiation nor polyphenol supplementation affected spleen weight. However, the results suggest that irradiation induced behavioral disturbances that were not ameliorated by dietary polyphenols. Additionally, irradiation generally reduced cell counts within the dentate gyrus and subventricular zones (suggesting reduced neurogenesis), and polyphenol supplementation generally increased cell counts (suggesting increased neurogenesis), although the factors did not significantly interact (i.e. polyphenol supplementation did not significantly protect the brain from the effects of proton irradiation).

Disclosures: A.D. Trofimova: None. N. Kalynovska: None. D.Y. Xu: None. H. Cao: None. M.S. Dulcich: None. N.M. Bajwa: None. D. Baylink: None. R.E. Hartman: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

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Program #/Poster #: 053.12/Y10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroprotective effect of curcumin against experimental short-term exposure to ozone in rat hippocampus evaluated by Fluoro-Jade C stain

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Abstract: Ozone (O₃) is one of the main tropospheric pollutants. The exposure to O₃ leads to the formation of reactive oxygen species (ROS). The hippocampus is highly sensitive to oxidative stress and undergoes pathophysiological changes. Curcumin (CUR) has multiple desirable properties as a neuroprotective drug, underlying its antioxidant, anti-inflammatory and anti-aggregant activities. Methods: Eighty male Wistar rats were used (n=20 per group). Four groups were employed: Intact Control (CI), CUR Control (CC), O₃ Control (CO) and treatment group (OC), then each group was subdivided in four exposure times; 1, 2, 4 and 8 hours (5 per subgroup). The CI group was exposed to O₃-free air without CUR; the CC group received the CUR supplementation (5.6 mg/Kg/day) for 7 days until the exposure to O₃-free air. The CO group was exposed to 0.7 ppm of O₃ without CUR and finally the therapeutic group (OC) was fed with CUR for 7 days until the exposure to 0.7 ppm of O₃. At the end of the exposure time, rats were intracardially perfused with phosphate buffer solution and fixed with 4% paraformaldehyde, and brains were extracted. Coronal hippocampal slices of 30 μm were performed in a vibratome. Neuronal degeneration was determined by Fluoro-Jade C (FJC) staining as described by Schmued (2005). The percentage of degenerative cells was obtained by counting the number of positive cells from a total of one hundred cells in 200x field amplification by triplicate. The CA1 region of the hippocampus was analyzed. Results were analyzed with the Kruskal-Wallis test followed by the U Mann-Whitney test, the significance level was set at p<0.05. Results and conclusions: The CO group showed a time-dependent increase in the percentage of positive cells with a greater presence of degenerative cells after 8 hours of exposure to O₃. The neuronal degeneration effect of O₃ starts at 2 hours of exposure compared to control groups (p<0.01). The OC group showed a decrease in the levels of FJC+

cells reaching levels similar to the CI and CC groups. This highlights the beneficial effect of CUR in preventing the process of neuronal degeneration caused by exposure to O₃.

Disclosures: S. Nery-Flores: None. H. Espinoza-Gutiérrez: None. M.L. Mendoza-Magana: None. M. Ramírez-Herrera: None. M. Romero-Prado: None. C. Vega-Román: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.13/Y11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Multiple Sclerosis Society RG-1607-25423 (MJB)
PO1 MH64570 (HAG)
R44 NS092137 (HAG)

Title: Role of prion protein in experimental autoimmune encephalomyelitis and neuroinflammation

Authors: *H. LI, M. J. BELLIZZI, J. W. HAMMOND, H. A. GELBARD
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Abstract: Prion protein in the misfolded pathogenic form is the well-known cause of prion diseases such as Creutzfeldt Jakob Disease (CJD). The biologic role of the cellular prion protein thought to be neuroprotective, but is not fully understood in neuroinflammatory conditions. We hypothesized that prion protein is downregulated during neuroinflammatory disease. To investigate this, we used a model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE), in 8 week old C57bl/6 mice of both sexes. EAE models subacute inflammatory changes in the central nervous system (CNS) associated with MS, including microglial activation (microgliosis), and degeneration of synapses. We studied the hippocampus grey matter degeneration as it contributes to progressive cognitive impairment in MS patients. Immunohistochemistry revealed down regulated prion protein in the CA1 pyramidal cells of the hippocampus with EAE correlated with microgliosis and synaptic loss. To determine if hippocampal neuroprotection in EAE restores prion protein expression we used URM-099, a broad spectrum mixed lineage kinase-3 (MLK3) inhibitor, and ibudilast, a phosphodiesterase inhibitor. URM-099 has been shown to prevent synaptic degeneration in EAE mice and Ibudilast has shown to slow brain atrophy in MS patients and has just passed phase II clinical trials. Hippocampal neuroprotection using URM-099 and ibudilast restore prion protein expression in EAE to levels comparable to controls. Our findings show that prion protein is down regulated in a proinflammatory milieu and loss of prion protein can contribute to neurodegeneration.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.14/Y12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: COBRE #4P30GM103340
Eye, Ear, Nose and Throat Foundation

Title: Neuroprotective lipid synthesis is enhanced in mesencephalic neurons at the onset of MPP+ induced cellular damage

Authors: *M. N. DREYER, J. M. CALANDRIA, N. G. BAZAN
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Abstract: Parkinson's disease is a neurodegenerative disease characterized by the death of dopaminergic neurons in the *substantia nigra pars compacta* of the midbrain. Biologically active metabolites of docosahexaenoic acid (DHA) including a novel class of mediators called elovanoids and Neuroprotectin D1 (NPD1), have demonstrated neuroprotective properties (Bhattacharjee et al, Sci. Adv. 2017; Jun et al, Sci. Rep. 2017). In retinal pigment epithelial cells, elovanoids display neuroprotective activity reflected in sustainment of photoreceptor cell integrity and prevention of apoptosis by enhancing the expression of pro-survival proteins. NPD1 prevented and rescued some of the deleterious effects of the neurotoxins including apoptosis, dendritic order, dendritic morphology, neurite radii, and neurite branching and total number of neurites (Calandria et al, Cell and Mol. Neurobiol. 2015). We hypothesize that elovanoids, a novel class of DHA derivatives are produced in dopaminergic neurons during early stages of cell damage to cope with and overcome uncompensated oxidative stress (UOS). To assess the role of DHA derivatives in the survival of dopaminergic neurons, we utilized a rat mesencephalic primary culture enriched in Tyrosine Hydroxylase (TH) positive neurons. The neurotoxin 1-methyl-4-phenylpyridinium (MPP+) was added to the culture to induce cell death to the dopaminergic neurons. The lipidomic profile of the culture was assessed using Liquid Chromatography-Mass Spectrometry. In two exploratory blinded experiments, we observed an increase in the NPD1 synthesis during the first 6 hours of treatment. MPP+ treated TH+ neurons displayed an increased cell death by Hoechst and TH immunostaining and showed reduced dendritic branching by Sholl analysis when compared with their control counterpart, showing the existence of apoptosis and retraction of dendritic architecture. Here, we demonstrate for the first time that primary mesencephalic neurons are able to respond to stress induced by MPP+ with an increase in the synthesis of bioactive lipids derivatives from DHA to delay or prevent apoptosis, and the addition of these mediators can enhance the effects of the ones synthesized

endogenously. Since elovanoids and NPD1 are active metabolites of DHA, and are both involved in neuroprotection, we believe elovanoids are molecular guardians involved in the neuroprotective mechanism that sustain homeostasis and survival in dopaminergic neurons at the onset of UOS. These findings advance the knowledge of the pro-homeostatic signaling and lays the basis to explore new therapeutic avenues.

Disclosures: M.N. Dreyer: None. J.M. Calandria: None. N.G. Bazan: None.

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.15/Y13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DTRA CB3943

Title: Assessing the effectiveness of gabapentin and d-leucine as anticonvulsants and neuroprotectants in acetylcholinesterase inhibited mice

Authors: *B. C. LAGER, K. LAITIPAYA, J. K. CHANDLER, D. D. PALMER, C. L. HONNOLD, E. A. JOHNSON
USAMRICD, Aberdeen Proving Ground, MD

Abstract: When exposed to soman (GD), a chemical warfare nerve agent (CWNA), acetylcholinesterase is inhibited and can initiate status epilepticus (SE), progressive brain damage and behavioral impairment. Currently approved benzodiazepine anticonvulsant treatments for CWNA exposure only have a short window of efficacy due to rapid inactivation of the inhibitory gamma-aminobutyric acid (GABA) pathway. Therefore, developing treatments that aid in lengthening that window or acting through alternate mechanisms to improve control of seizure post nerve agent exposure. Two potential adjuncts to current treatments are gabapentin, an anti-epileptic and neuropathic pain treatment and D-Leucine, the biologically inactive enantiomer of the branched chain amino acid (BCAA) leucine, which can terminate ongoing seizures more effectively than diazepam in the kainic acid seizure model. This study was designed to evaluate whether gabapentin or D-leucine, in conjunction with currently fielded treatments, can reduce mortality, severity of brain injury, and seizure activity. Seizure dynamics, such as progression and magnitude, were measured by electroencephalographs (EEG) on telemetry implanted mice. Mice received the oxime HI-6, atropine (both methyl nitrate and sulfate) as standard treatment then received either gabapentin or D-leucine in conjunction with a sub-effective dose of midazolam 40 minutes after seizure onset. Gabapentin and D-leucine reduce mortality in mice exposed to GD and show potential as neuroprotectants and anticonvulsants when administered after exposure. The views expressed in this talk are those of

the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. These studies were funded by the Defense Threat Reduction Agency (DTRA). Brianna Lager was supported in part by an appointment to the Research Participation Program for the U.S. Army Medical Research and Materiel Command administered by the Oak Ridge Institute for Science Education through an agreement between the U.S. Department of Energy and U.S. Army Medical Research and Materiel Command.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.16/Y14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Evaluation of cannabinoids for anticonvulsant and antiepileptic efficacy in a rat model of soman-induced status epilepticus

Authors: ***B. MARRERO-ROSADO**¹, F. ROSSETTI², C. SCHULTZ¹, E. KUNDRICK¹, M. STONE¹, S. O'BRIEN¹, K. WALKER¹, L. LUMLEY¹

¹US Army Med. Res. Inst. of Chem. Def., Aberdeen Proving Ground, MD; ²Blast Induced Neurotrauma Br., Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Cannabinoids have beneficial effects in multiple animal models of seizure. Exposure to soman (GD), a chemical warfare nerve agent, induces *status epilepticus* (*SE*) which becomes refractory to benzodiazepines if the anticonvulsant treatment is delayed. The resulting prolonged and severe *SE* causes extensive neuronal damage and cognitive impairment, and can lead to the development of spontaneous recurrent seizures (SRS). We previously reported that acute administration of JZL195, which increases endocannabinoids in combination with midazolam, reduces seizure activity. We currently report on the efficacy of acute and repeated administration of JZL195 or of cannabidiol in rats with soman-induced *SE*. Rats were treated with atropine sulfate and HI-6 1 min after GD exposure and with midazolam 40 min after seizure onset. In one experiment, the administration of CBD as a single pretreatment at 30–60 minutes prior to GD reduced the number of animals that developed SRS, while earlier administration 120 minutes prior to GD was not effective at reducing SRS incidence. In a second experiment, a 2-hour pretreatment with CBD was followed by repeated CBD or drug vehicle at 6 hours after GD

exposure, and additional daily treatments of CBD for 3 days following GD-induced *SE*. Only rats exposed to GD and administered CBD at the 6-hour time point had significantly reduced seizure duration during the first 3 days after GD-induced *SE*, reduced incidence of epileptogenesis, and a significant decrease in the number of SRS events. In a third experiment, rats administered the synthetic cannabinoid WIN 55,212-2 with midazolam as a delayed combination therapy following exposure to GD or those administered repeated JZL195 had exacerbated epileptic activity. Altogether, data suggest that cannabinoids can reduce the seizurogenic effects of GD poisoning when administered as a pretreatment and continuously during the days following prolonged *SE*. This research was supported by an NIH Interagency Agreement with the USAMRICD.

The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense or the US Government. The experimental protocol was approved by the Animal Care and Use Committees at the US Army Medical Research Institute of Chemical Defense (USAMRICD), and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.17/Y15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Curcumin reduces neurodegeneration in rat hippocampus induced by experimental short-term exposure to ozone

Authors: **H. ESPINOZA-GUTIÉRREZ**¹, **S. NERY-FLORES**¹, ***M. A. RAMIREZ-HERRERA**², **M. L. MENDOZA-MAGAÑA**¹, **C. CORTEZ-ALVAREZ**¹, **R. BONNET-LEMUS**¹, **A. RAMIREZ-MENDOZA**¹

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Abstract: Ozone (O₃) is one of the major urban air pollutants. The exposure to O₃ leads to the formation of Reactive Oxygen Species (ROS) that reach the hippocampus through the olfactory bulb. In the brain, oxidative damage mediated by ROS is associated with neurodegeneration. Neurodegeneration due to oxidative damage is characterized by biochemical changes such as the oxidative modification of proteins, so these macromolecules undergo structural and functional loss, producing amorphous disintegrative debris. Curcumin (CUR) is a natural polyphenol that has antioxidant properties because acts as a ROS scavenger and might protect neurons from

oxidative damage. This work evaluates capability of CUR to inhibit the neurodegeneration induced by experimental short-term exposure to O₃ in rat hippocampus. Methods: Twenty one days old male Wistar rats were distributed into four experimental groups: Intact Control (CI), CUR Control (CC), O₃ Control (CO) and treatment group (OC), then each group was subdivided in four different exposure times, (1, 2, 4 and 8 hours), which led to 5 rats per subgroup. CO and OC groups were exposed once to O₃ at 0.7 ppm while CC and OC received a daily dose of 5.6 mg CUR/kg for 5 days as a supplemented diet. Finally, CI group did not receive any treatment nor O₃ exposure. After exposure, rats were sacrificed and the brains were fixed and dissected. Subsequently, coronal sections of the hippocampus (30 µm) were performed in a vibratome. The silver stain described by De Olmos (1994) with minor modifications, was used to evaluate neurodegeneration. Positive neurons were counted in the CA1 region. The results were statistically analyzed. The significance level was set at p<0.05. Results and conclusions: The CO group presented a higher number of positive neurons compared to the other controls groups (p<0.001). OC group showed a decreased number of positive cells compared to CO group from 2 hours to 8 hours (p<0.001). Also CI and CC groups didn't show positive neurons. These results suggest that therapeutic dietary administration of CUR decrease neurodegeneration after exposure to an oxidizing pollutant such as O₃.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.18/Y16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Cepham, Inc.

Title: Neuroprotective and antioxidative efficacy of a unique combination of standardized herbal extracts of *huperzia serrata* (cogniup), *convolvulus pluricaulis* and *celastrus paniculatus*

Authors: *I. S. AHMAD¹, A. SWAROOP², M. BAGCHI², D. BAGCHI³

¹Cepham Life Sciences, Inc., Linthicum Heights, MD; ²Cepham, Inc., Somerset, NJ; ³Pharmacol. & Pharmaceut. Sci., Univ. of Houston Col. of Pharm., Houston, TX

Abstract: Physical, environmental and work stress in conjunction with hectic lifestyle and unhealthy food habits are the major cause of diverse neurodegenerative disorders including cognitive decline, memory impairment and Alzheimer's diseases. Oxidative neuronal injury and acetylcholine deficiency have a major impact on learning and memory. The majority of the

treatment strategies are based on the improvement of cholinergic function in the brain and one of the emerging therapeutic target is to enhance the acetylcholine level in the brain. Standardized botanical extracts including *Huperzia serrata*, *Convolvulus pluricaulis* (Shankhapushpi; SP) and *Celastrus paniculatus* (Jyotismati; JY) have been demonstrated to attenuate brain function by serving as a natural acetylcholinesterase inhibitor and exhibited their efficacy in the management of neurological impairment, dementia and Alzheimer's disease. We have developed a novel, *Huperzia serrata* extract enriched with 1% Huperzine A (Cogniup), which demonstrated broad spectrum safety and neuroprotection. In this study, a unique combination of CogniUp, SP and JY (MZ001) was developed, which effectively and synergistically inhibited acetylcholinesterase (AChE) and attenuated oxidative stress. Concentration-dependent AChE inhibition kinetics was assessed individually using 0, 3.0, 6.0, 9.0, 12.0 and 24.0 mg SP/ml, and 0, 0.5, 1.0, 2.0, 4.0 and 8.0 mg JY/ml, and 0, 0.0625, 0.125, 0.25 and 0.5 µg CogniUp/ml. It was observed that a combination of SP, JY and CogniUp (12 mg/ml, 4 mg/ml and 0.125 µg/ml) provided the most efficacious and synergistic AChE inhibition. In another independent study, cultured pheochromocytoma PC-12 cells were pre-incubated with Cogniup (0, 0.0625, 0.125, 0.25 and 0.5 µg/ml) and a combination of SP, JY and Cogniup (12 mg/ml, 4 mg/ml and 0.125 µg/ml) (MZ001) followed by an oxidative exposure to 200 µM of H₂O₂ over the period 0-48 hours. Pretreatment of these cells with Cogniup or MZ001 prior to H₂O₂ exposure significantly elevated the cell survival, increased the levels of reduced glutathione and catalase, and reduced lactate dehydrogenase leakage and malondialdehyde level. Our results indicate that Cogniup and MZ001 exhibited dramatic neuroprotective effect against H₂O₂-induced oxidative damage, which may be important for clinical efficacy for the treatment of neuronal injury. Further studies are in progress to establish the therapeutic efficacy of MZ001 in neuroprotection.

Disclosures: **A. Swaroop:** A. Employment/Salary (full or part-time);; Cepham, Inc. **M. Bagchi:** 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.; Cepham, Inc. **D. Bagchi:** 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.; Cepham, Inc..

Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.19/Y17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroprotective effect of dexamethasone administration on neural damage and seizures induced by kainic acid in rats

Authors: *V. BARON-FLORES¹, A. DIAZ-RUIZ², C. JIMÉNEZ-HERNÁNDEZ¹, Á. PÉREZ-JUÁREZ¹, J. LANDA-COVARRUBIAS¹, M. ROMERO¹, C. RIOS³

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Abstract: Epilepsy is one of the most prevalent neurological disorders, affecting 1% of the world population, and it is caused by the abnormal discharge of neurons in the brain. Among the different types of the disease, temporal lobe epilepsy (TLE) is the most frequent and represents the main pharmaco-resistant form of epilepsy. One of the strategies to reduce neuronal damage is neuroprotection, a set of strategies that aim to stop the inflammatory and metabolic cascade after seizures. The leading mechanisms of damage are, oxidative damage, inflammatory response as a result of the blood-brain barrier breakdown, events triggering apoptosis. Dexamethasone (Dx) belongs to the group of glucocorticoids, used in the treatment of inflammatory and autoimmune diseases and in the transplantation of organs and tissues. Dx inhibits the immediate mechanisms of inflammation, thus, it is a useful tool to understand the participation of inflammatory response after seizures and its role in neuroprotection. Male Wistar rats employed four groups of rats: Animals treated with: 1) saline solution i.p., 2) dexamethasone 2mg/Kg i.p. (both groups were administered every 24 h for five consecutive days, as a pretreatment) 3) Kainic acid (KA) 10mg/Kg i.p, and 4) dexamethasone 2mg/Kg and KA 10mg/Kg, The intensity of seizures displayed by rats was evaluated for two hours after KA injection, using the Racine score. The levels of glutathione (GSH) and Lipid peroxidation (LP) in the hippocampus of animals were also evaluated. We observed that Dx pretreatment antagonized the reduction of GSH levels and the enhancement of LP caused by KA administration. An increased latency and a decrease in the severity of seizures was also observed by effect of Dx pretreatment. Therefore, it is proposed that Dx, as a pretreatment, is neuroprotective and able to attenuate seizures in the KA-induced model in rats.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.20/Y18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Small molecule inhibitors of SARM1 prevent axon degeneration

Authors: R. KRAUSS, *T. M. ENGBER, R. DEVRAJ, T. BOSANAC, R. HUGHES
Disarm Therapeut., Cambridge, MA

Abstract: A variety of toxic, metabolic and genetic insults to peripheral nerves lead to acute injury or chronic disease, including chemotherapy-induced and diabetic peripheral neuropathies as well as genetic disorders such as Charcot-Marie Tooth. Although evidence indicates that these disorders are primarily the result of damage to axons, there are currently no axonal protective therapies. SARM1 has been identified as the central mediator of a cell-autonomous program of axonal dismantling leading to Wallerian degeneration and loss of function. Animal models of chemotherapy-induced and diabetic peripheral neuropathies in SARM1 *-/-* mutant mice have shown robust axonal protection and preservation of neural function, thus confirming that SARM1 is an attractive target for development of novel treatments for these disorders. Injury to axons activates SARM1 NADase activity, causing a rapid depletion of axonal NAD⁺ levels and triggering the axonal dismantling program. We have screened a small molecule library to identify inhibitors of SARM1 enzymatic activity in a biochemical assay. With these screening hits as a starting point, we have developed potent SARM1 inhibitors that protect murine DRG axons *in vitro* from mechanical, chemical and metabolic damage, reproducing the SARM1 *-/-* axonal protective phenotype. We have also established SARM1-dependent peripheral and central axonal injury models to test efficacy and pharmacodynamic response of our drug candidates *in vivo*. SARM1 inhibitors have the potential to prevent axonal degeneration in peripheral and central neuropathies and provide a novel disease-modifying treatment for these disorders.

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.21/Z1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Canadian Institutes of Health Research
Diabetes Canada
Department of Medicine
Faculty of Medicine and Dentistry
University Hospital Foundation,

Title: The Role The role of RAC1 during adult peripheral axonal regeneration

Authors: *P. KOMIRISHETTY¹, C. CHENG³, D. W. ZOCHODNE²

²Med. and Neurol., ¹Univ. of Alberta, Edmonton, AB, Canada; ³Univ. of Calgary, Calgary, AB, Canada

Abstract: Peripheral nerve damage from trauma or neuropathy is common and irreversible. Manipulation of specific molecules that influence growth cone behavior and peripheral neuron plasticity may offer therapeutic options. Rho GTPase family effectors play an important role in various aspects of neuron development and regeneration. RAC1 (Ras-related C3 botulinum toxin substrate 1), is a Rho GTPase family member known to regulate neurite outgrowth and cytoskeleton architecture operating through effectors that include MAPK. Despite the importance of Rac1 in growth cone dynamics, its direct role in axonal regeneration during peripheral axonal regeneration has not been evaluated. Expression of the RAC1 protein and its mRNA was confirmed in intact sciatic nerves and dorsal root ganglia (DRGs). RAC1 mRNA levels in DRGs increased after distal axotomy, indicating a role in preparing sensory neurons for enhanced plasticity during regeneration. Moreover, RAC1 expression was also confirmed in complex growth cones of regenerating axons. RAC/CDC42 Activator II, an epidermal growth factor (EGF) has been used to activate RAC1 in dissociated adult peripheral sensory neurons from DRGs. This approach activated RAC1 in a dose-dependent fashion. Neurite outgrowth *in vitro* in uninjured and injured adult sensory neurons was measured. Both adult SD rat uninjured and injured dorsal sensory neurons *in vitro* demonstrated a dose-related increase in neurite outgrowth and the number of sprouting neurons when exposed to the RAC1 activator, indicating an ongoing functional role during adult regeneration. Taken together, the findings identify a role for RAC1 in adult sensory neurons with localization both in perikarya and growth cones and evidence for functional activity. [Supported by CIHR, CDA, DoM, FoMD, UHF]

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Poster

053. Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 053.22/Z2

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R21 NS101652
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Title: Regulation of hypoxia tolerance in *Drosophila melanogaster* by activating notch in neuronal and glial cells

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Abstract: Hypoxia represents a critical element in the pathogenesis of many human diseases, such as ischemic stroke, myocardial infarction and solid tumors. Understanding the mechanisms regulating hypoxia tolerance or susceptibility is essential in developing effective strategies for medical interventions. Our previous studies and those of others revealed that Notch signaling regulates hypoxia tolerance in both *Drosophila melanogaster* and humans. However, the mechanistic details are largely unknown. We have found that specific activation of Notch in neuronal and glial cells in the CNS of *Drosophila melanogaster* rescues hypoxia-induced lethality and confers hypoxia tolerance *in vivo*. In the current study, we developed a novel dual-USA/Gal4 system to determine the critical genetic interactions between Notch signaling and other candidate genes in terms of hypoxia tolerance. This system allowed us to activate Notch signaling in the Eaat1 positive glial cells, which dramatically enhances hypoxia tolerance in fruit flies, and, simultaneously, knockdown a candidate gene in the same glial cells. Using this system, we discovered that Notch activation requires evolutionarily conserved genes (i.e., HES1/hairy, FOXC1/croc and ZNF521/Oaz) to regulate hypoxia tolerance. Interestingly, we also found that knocking-down KCND2/Shal and EGFR/Egfr confers hypoxia tolerance in a Notch-independent manner. In summary, activating Notch signaling in neuronal and glial cells regulates hypoxia tolerance *in vivo*. We also identified evolutionarily conserved, Notch-dependent and independent mechanisms regulating hypoxia tolerance. These mechanisms have strong potential to be translated into humans and serve as novel targets for developing therapeutic strategies to treat hypoxia-related diseases.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.01/Z3

Topic: C.09.Stroke

Support: AHA Beginning Grant-in-Aid
NS079153

NS075035
NS097000
NS101718

Title: Co-expressed gene networks associated with intracerebral hemorrhage and peri-hematoma edema volumes following human ICH: Search for potential therapeutic targets

Authors: ***B. STAMOVA**, M. DUROCHER, B. P. ANDER, G. JICKLING, F. HAMADE, X. ZHAN, D. LIU, X. CHENG, H. HULL, N. SHROFF, A. YEE, F. R. SHARP
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Abstract: Objectives: Intracerebral hemorrhage (ICH) is a devastating disease with high morbidity and mortality and represents 10-15% of all strokes. Determinants of outcome are significantly influenced by hematoma and peri-hematoma edema (PHE) volume and expansion. Following the acute phases of ICH that include evolution of cerebral edema, a complex cascade of local and systemic cellular immunity develops. This deleterious multi-systemic response leads to cellular injury and apoptosis following ICH. Identifying candidate modulators that influence ICH and PHE volumes may serve as therapeutic targets to improve clinical outcomes. We performed gene co-expression studies in peripheral blood to examine the immune response following ICH with respect to ICH and PHE volumes. **Methods:** Whole-genome RNA expression from 20 ICH subjects (14M/6F) was assessed on Affymetrix HTA 2.0 microarrays. Volumetric measurements were conducted on CT images using AnalyzePro 1.0 software (AnalyzeDirect, Inc.). Weighted Gene Co-expression Network Analysis (WGCNA) was performed to define modules of co-expressed genes (parameters included: soft-thresholding power $\beta=11$; unsigned network; *cutreeDynamic* with method="tree"). A correlation test was processed in R to find significant relation to PHE or ICH volume with $p<0.05$. **Results:** 4 modules were positively correlated to PHE volume. 3 modules were correlated to ICH volume – 2 positively and 1 negatively. Two volume-associated modules were significant for both ICH and PHE volumes. Genes in these two modules were associated with multiple inflammatory pathways such as the Inflammasome Pathway, NFAT Regulation of Immune Response, IL-17, NF-kB, p38MAPK, ERK5, Toll-like Receptor (TLR) Signaling and FCgamma-receptor mediated monocyte and macrophage phagocytosis. ERK5/MAPK cascades play important roles in many cellular processes involving cellular proliferation, differentiation, apoptosis, and neuronal survival. TLR signaling in resident microglia and peripheral infiltrating leukocytes has been demonstrated following ICH-related brain injury and is associated with poor clinical outcomes. Scavenger mechanisms involving FCgamma-receptor mediated monocyte and macrophage phagocytosis has been implicated in hematoma resolution. Oxidative stress pathways (iNOS Signaling and Production of Nitric Oxide and other Reactive Oxygen Species; Growth Factor Signaling) were also identified. **Conclusions:** WGCNA revealed modules of co-expressed genes associated with key predictors of outcome following ICH – ICH and PHE volumes. The most-interconnected genes (hubs) may present potential novel therapeutic targets.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Program #/Poster #: 054.02/Z4

Topic: C.09.Stroke

Support: Cooperative Research Program for Agriculture Science & Technology Development (PJ012551, PJ0125512018)
National Research Foundation of Korea NRF-2016R1A2B4008316

Title: New Near-infrared dye for BBB disruption assessment

Authors: J. KIM, 501-747, M. PARK, 501-747, K. CHOI, 501-747, *H. KIM
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Abstract: Background: Since it is known that serum albumin-bound dyes can cross the blood-brain barrier (BBB) after ischemia, Evans Blue dye is commonly used to assess BBB disruption because of its rapid binding to serum albumin. In addition, indocyanine green (ICG), a clinically available dye, binds to serum proteins that could also be used for assessment of BBB impairment. Unlike these near-infrared (NIR) dyes, zwitterionic NIR fluorophore (ZW800-1) shows no serum binding, ultralow non-specific tissue uptake, and rapid elimination from the body via renal filtration. In this study, we report the use of ZW800-1 as a NIR fluorescence imaging agent for detecting BBB disruption in rat stroke models. Methods: Three types of NIR fluorophores, Evans Blue, ICG, and ZW800-1, were administered intraperitoneally into rat photothrombotic stroke models by using 4% concentration of each NIR dye. The NIR fluorescence signals in the infarcted brain tissue and biodistribution were observed in real-time using the Mini-FLARE® imaging system up to 24 h post-injection. Results: ZW800-1 provided successful visualization of the ischemic injury site in the brain tissue, while the remaining injected dye was clearly excreted from the body within a certain period of time. Although Evans Blue and ICG provided mapping of the infarcted brain lesions, they exhibited high non-specific uptake in most of the tissues and organs and persisted in the body over 24 h post-injection. Conclusion: Our results suggest the promising application of ZW800-1 as a new strategy in BBB experiments and future therapeutic development.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

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Topic: C.09.Stroke

Support: MEXT KAKENHI Grant Number JP23700620
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Title: A study of hierarchical factor structure of stroke patients with cognitive dysfunction using behavioral assessment

Authors: *Y. IWASAKI¹, K. GORYO²

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Abstract: Introduction: Post-stroke cognitive dysfunction is a common symptom of stroke and can have a significant effect on a patient's ADL (Activities of Daily Living). Neuroimaging and neuroanatomical studies have identified the cortical association areas related to cognitive function. However, it is difficult to adequately evaluate how post-stroke cognitive dysfunction affects ADL. The purpose of this study is to more effectively extract clinical characteristics of patients suffered with cognitive dysfunction through behavior on ADL. Method: Thirty occupational therapists selected 245 evaluation items from FIM (Functional Independence Measure) relevant to the difficulty in ADL. The items were analyzed using multidimensional scaling method and cluster analysis, resulting in 6 groups consisting of 66 items. On the basis of the items, 180 stroke patients with cognitive dysfunction were evaluated with 5 grades. Moreover coma grades (Japan Coma Scale: JCS), FIM and neuropsychological examination (MMSE) were checked. Analytical methods were carried out as follows: 1) factor analysis to the 66 items, 2) correlation between the extracted factors and the days after onset, FIM, and MMSE, and 3) multiple regression analysis between extracted factor scores as dependent variable and, the days after onset, JCS, FIM, and MMSE as independent variable. Result: Factor analysis revealed relevant 8 main factors with total 46 subsystem items with confidence coefficient 0.849~0.980: 1) situation judgment (6 items), 2) memory (7), 3) perseveration (5), 4) arousal (5), 5) behavioral regulation (5), 6) sustained attention (5), 7) selective attention (7), and 8) communication (6). Factors 1 to 8 were strongly correlated with consciousness and FIM ($r=0.322\sim0.652$, $p<0.001$). We investigated dependent variables of JCS, MMSE and FIM score, Independent variable Behavioral Scale Factors 1~8 with multiple regression analysis. Factor 1 correlated to independence of ADL ($p<0.05$), and Factor 4 to consciousness ($p<0.01$). Conclusion: We revealed 8 main factors in assessment factors of cognitive dysfunction. The hierarchical structure is exhibited among factors. Those hierarchical factors would be important to efficaciously evaluate stroke patients with cognitive dysfunction. Observational evaluation

could understand the clinical feature of patients with cognitive dysfunction substantially. We could provide better therapy for cognitive dysfunction by strengthening relationships with assessment factors of cognitive dysfunction and neuroimaging and neuroanatomical studies.

Disclosures: Y. Iwasaki: None. K. Goryo: None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.04/Z6

Topic: C.09.Stroke

Title: Nogo-A neutralization enhances VEGF-mediated angiogenesis and functional recovery after stroke

Authors: *R. RUST^{1,2}, C. GANTNER¹, A. ENZLER¹, A. SIEWERT³, L. GRÖNNERT⁴, D. KUKELOVA¹, M. A. MAURER², M. E. SCHWAB^{5,2}

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Abstract: The neurite outgrowth inhibitor Nogo-A acts as a negative regulator of CNS angiogenesis in development. It interacts with the sphingosine 1-phosphate receptor 2 (S1PR2) restricting both neural and vascular growth. However, its function on vascular repair after CNS injuries has not been investigated yet. Here, we show that endothelial S1PR2 is upregulated after stroke and is surrounded by high Nogo-A signal in the injured forebrain cortex. Genetic deletion of either Nogo-A or S1PR2 resulted in a significantly higher density of regenerating vessels in the ischemic border zone. These animals also showed an improved functional performance (forelimb placement on irregular ladder; cylinder test) compared to wildtype controls three weeks after stroke. Behavioral improvements strongly correlated with the high levels of vascular repair after stroke but not with stroke volumes. Blocking angiogenesis with anti-VEGF antibodies in Nogo-A deleted animals led to lower capillary density in the ischemic border zone and canceled the improved behavioral performance. These results show that blocking the Nogo-A pathway is beneficial for post-stroke angiogenesis and functional recovery. We hypothesize that Nogo-A and S1PR2 deletion may protect specific neuronal cells and connections from ischemic damage by accelerating blood vessel repair in the brain. Ultimately, targeting Nogo-A by immunotherapy may provide a new and clinically relevant strategy to improve CNS perfusion after ischemic injuries.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Program #/Poster #: 054.05/Z7

Topic: C.09.Stroke

Support: NIH Grant R01NS093057

Title: Investigating contralesional cortical activation with cellular resolution in post-stroke recovery

Authors: *T. C. CHIANG, M. ITO, S. HARVEY, M. Y. CHENG, G. K. STEINBERG
Neurosurg., Stanford Univ., Stanford, CA

Abstract: Background: Functional neuroimaging studies have reported increased activation in the contralesional cortex in both experimental and clinical settings of stroke. However, the cellular resolution of contralesional cortical activity in post-stroke recovery is unclear. In this study we characterized the time course of contralesional cortical activation during post-stroke recovery using activity-dependent markers. Methods: Adult male C57Bl6 mice (11-13 weeks) were subjected to transient middle cerebral artery occlusion (MCAO). Stroke lesion was verified at post-stroke day (PD) 3 by T2-weighted MRI and/or histology. Mice with infarcts in both cortical and striatum were included in the study. Brains were collected at PD3, 7, 15, and 28 and were processed for immunostaining using Early growth response 1 (Egr1), an activity-dependent marker. PD7 and 15 brains were co-stained with neuronal marker NeuN and GABAergic marker parvalbumin. Naïve mice were prepared as no stroke control. Egr1 positive cells in the primary motor cortex (M1), pre-motor cortex (M2), and somatosensory cortex (SS) in the ipsi- and contralesional hemisphere were quantified. Results: Naïve mice showed similar Egr1 expression in both cortical hemispheres. Time-course analysis revealed that Egr1 expression in the contralesional cortex was significantly upregulated at PD7 and 15, and returned to basal levels by PD28. Furthermore, Egr1 expression was significantly higher in the contralesional than the ipsilesional cortex at PD7 and 15. Region-wise in-depth analysis revealed that these changes occurred at contralesional M2 and SS, but not in the M1. All Egr1 positive cells were NeuN-positive, but parvalbumin-negative. Conclusions: Our results suggest that increased contralesional cortex activation occurs after stroke, particularly in somatosensory and pre-motor cortex but not in the primary motor cortex, suggesting a potential active role of these cortical regions in stroke recovery. Ongoing studies are elucidating the neuronal subtypes of activated Egr1 cells in the contralesional cortex using various excitatory and inhibitory markers.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

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Program #/Poster #: 054.06/Z8

Topic: C.09.Stroke

Title: Upregulated interferon α/β signaling pathways are related to developing intracranial aneurysm in human and rat animal model

Authors: *T. YOKOI¹, S. ISHIDA², T. ISONO¹, T. CHANO¹, K. NOZAKI¹

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Abstract: Though the Intracranial Aneurysm (IA) can rupture and cause Subarachnoid Hemorrhage (SAH) leading to death, Robust Clinical criteria of preventive intervention for Unruptured IA (UIA) including biomarker of UIA has yet to be defined precisely and there remains much room to elucidate molecular mechanisms or events in developing IA.

The purpose of this study is to determine crucial molecules in cells of developing UIAs which may result in rupture.

We prepared the arterial wall samples of UIAs and superficial temporal arteries as normal control from human patients during their operations. After RNA extraction, we compared gene expression of these specimen with Next Generation Sequencer(NGS) technique. Analysis of global transcriptome or RNA-seq showed up-regulation of interferon-alpha (IFN-alpha) and interferon-beta (IFN-beta) related genes. (IFI6, IFIT1, IRF8, ISG15, OAS3) Quantitative RT-PCR were done to confirm and quantify the genes up-regulated in the IFN-alpha/beta signaling pathway detected in the NGS analysis. Immunohistochemistry of Rat aneurysm model showed expression of these genes mainly in the area with fragmentation or disappearance of internal elastic lamina.

Up-regulated interferon-alpha/beta signaling pathways may relate to developing intracranial aneurysm in human and animal model. The molecules in these pathways may be main targets in searching therapeutic intervention of UIA and biomarkers of UIA.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Title: First-in-human study of safety, tolerability and pharmacokinetics of novel neuroprotectant YC-6 after single ascending doses in healthy chinese subjects

Authors: X. CHEN¹, Q. ZHAO¹, Z. WANG¹, J. JIANG¹, G. YAN², *S. LIN³, P. HU¹

¹Phase 1 Unit, Clin. Pharmacol. Res. Ctr., Peking Union Med. Col. Hospital, Peking Union Med. college & Chinese Acad. of Med. Sci., Beijing, China; ²Zhongshan Sch. of Med., Sun Yat-Sen Univ., GuangZhou, China; ³Neurosci. Discovery, Guangzhou Cellprotek Pharmaceut. Co. Ltd., Guangzhou, China

Abstract: Objective YC-6, a synthetic steroid 5 α -androst-3 β ,5,6 β -triol, is a novel neuroprotectant and this is the first in human study to evaluate the safety, tolerability, and pharmacokinetics of single intravenous administration of YC-6 in healthy Chinese subjects. Methods This was a randomized, double-blind, placebo-controlled study with single intravenous injection of YC-6 in healthy subjects. A total of 61 participants were enrolled the study. Eight dose groups were designed in this study. *Single dose of YC-6 were 1.25 mg, 5 mg, 20 mg, 60 mg, 120 mg, 240 mg, 480 mg, or 720 mg.* All four subjects in the 1.25mg dose group received YC-6. Starting from the 5mg dose group, each subject was randomly received YC-6 or placebo at ratio of 6:2. Safety and tolerance were evaluated based on occurrence, frequency, and severity of adverse events (AEs). Routine clinical laboratory tests, 12-electrocardiograms (ECGs), physical examinations, and vital signs were performed at scheduled time points. AEs were monitored throughout the study, from the initial administration to 14 days post dose. Results 1. Safety results A total of 60 participants were completed the study. Eighteen AEs were reported in 16 subjects and the incidence was 26.7%. Among them, 17 AEs were judged mild and one were moderate, the moderate one was not drug-related. Twelve subjects in the YC-6 groups reported 14 AEs, the incidence was 26.09%, and 4 participants in the placebo group reported 4 AEs and incidence rate was 28.57%. The common AEs were found in various laboratory tests, such as mild transaminase increased. There were no clinically significant changes in any subjects in physical examination, laboratory test, and ECG reports before and after the administration of YC-6. All of the AEs were transient in nature and were resolved without any medical treatment.

2. Pharmacokinetic results. After intravenous injection of YC-6, the plasma concentration of YC-6 in each dose group increased rapidly and reached peak at the end of the intravenous administration (30-32 min). Mean total plasma CL and V_z were 52.47-77.16 L/h and 153.05-363.44L. $t_{1/2}$ was 1.42-4.17h. The increment of AUC and C_{max} was approximately dose-proportional in the dose range from 1.25 mg to 720 mg. The excretion of parent drug via urine and feces was less than 5% and 21.3% of dose respectively. Conclusion The single intravenous dosing of YC-6 in healthy Chinese volunteers produced a consistent and predictable pharmacokinetic profile. Systemic exposure to YC-6 increased in a dose proportional manner for dose range from 1.25mg to 720 mg. Single intravenous dosing of YC-6 up to 720mg was also found to be safe and well tolerated in healthy Chinese volunteers.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Title: The anesthetic propofol alleviates neuronal injury after ischemic stroke in mice

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Abstract: According to recent clinical progress, about 20% of stroke patients are eligible for endovascular procedures or a mechanical thrombectomy. These patients are subjected to general anesthesia while the influence of the anesthetic procedure after ischemic stroke has rarely been studied. In the investigation, we hypothesized that a clinically common anesthetic propofol could show neuroprotective effects following ischemic stroke. C57BL/6 male adult mice were subjected to a focal cerebral ischemic insult to the sensorimotor cortex. Propofol (30 mg/kg, i.p.) or vehicle was administrated from the onset of reperfusion upon the release of transient ligations of bilateral common cerebral arteries (CCAs). Propofol anesthesia was maintained for the next 3 hrs. At 3 days after stroke, staining with 2,3,5-triphenyl tetrazolium chloride of brain sections revealed reduced infarct volume in stroke mice received propofol anesthesia compared to vehicle

controls. Real-time quantitative polymerase chain reaction (RT-PCR) showed an increase of CD86 over time in the stroke animals after propofol treatment. In long-term neurological functional assessments, the adhesive removal test and the corner test were performed to evaluate sensorimotor deficits at 14 and 21 days after ischemic stroke. Stroke animals received propofol treatment exhibited better performance compared to stroke vehicle control mice. These results highlighted the assumption that propofol has a neuroprotective property to ameliorate ischemia-induced brain injury which may benefit early or delayed surgical procedures after ischemic stroke.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Topic: C.09.Stroke

Support: Japan Agency for Medical Research and Development
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Title: Comparison of functional brain connectivity before and after complex approach of KiNvis and BMI to patients with severely impaired chronic stroke. -A primary analysis of the resting state functional MRI-

Authors: *F. KANEKO^{1,2}, K. SHINDO^{1,2}, M. YONETA^{1,2}, M. OKAWADA^{1,2}, K. AKABOSHI^{1,2}, M. LIU¹

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Abstract: We have developed the system that provides kinesthetic illusion induced by visual stimulus (KiNvis). The KiNvis causes short-term excitability change of the corticospinal tract and kinesthetic perception using repetitive movements of the digital image from a first-person point-of-view. On the other hand, our research group reported a number of studies that the brain-computer interface paradigm improves functional recovery in patients with severe paralysis. The purpose of this study is to explore the brain functional change before and after complex therapeutic approach of KiNvis and BMI in patients with chronic stroke from the aspect of brain functional connectivity during resting state (rsFC). Fourteen patients (16-65 yrs old) participated. All patients presented severely impaired motor and/or sensory function. The Institutional Ethics Committee of the Hospital approved the study, and all patients signed an informed consent prior to participation. We applied a treatment package, which was composed of KiNvis therapy with

neuromuscular electrical stimulation, BMI therapy, and exercise for upper extremity for a total of 10 days. All patients were assessed their sensory-motor function using Fugl-Meyer Score (FMA), and modified Ashworth scale (MAS) before and after the treatment package. fMRI measurement during resting-state was performed before and after the intervention. At each session, whole brain images were collected using a T2*-weighted gradient-echo echo-planar imaging sequence using a 1.5T scanner. Preprocessing steps included spatial realignment to the mean volume of a series of images, normalization into the same coordinate frame as the MNI template brain, band-pass filtering, and smoothing. For each individual, brain masks were generated for tissue-based regression. Correlation analysis was performed from the average BOLD signal extracted from each ROI. Paired t-tests were performed to identify changes in z-transformed connectivity in each ROI pair before versus after the treatment. FMA and MAS for upper extremity significantly improved after the intervention. There were significant differences of rsFC before and after the intervention regarding a number of pairs between ROIs. The insula lobe had significantly higher connectivity to BA6 in the involved hemisphere, and BA44 and rolandic operculum in the uninvolved hemisphere after the intervention. rsFC of BA6 in the involved hemisphere and the fusiform gyrus in the involved and uninvolved hemisphere were enhanced after the intervention. The functional improvements in the participants were indicated, and in parallel, rsFC changed in the networks associated with the intervention.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.10/Z12

Topic: C.09.Stroke

Title: Long-term treatment with recombinant human soluble thrombomodulin improves ischemic brain damage via regulating systemic HMGB1 levels in mice

Authors: ***T. NAKANO**¹, **Y. NAKAMURA**², **K. IRIE**¹, **Y. YAMASHITA**¹, **T. MYOSE**¹, **K. MATSUO**¹, **H. KAMIMURA**¹, **H. ISHIKURA**², **Y. TAKASE**¹, **K. SANO**¹, **T. EGAWA**¹, **K. MISHIMA**¹

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Abstract: Background: Treatment with recombinant human soluble thrombomodulin (rhsTM) decreases infarct volumes and systemic high-mobility group box 1 (HMGB1) levels when rhsTM is bolus-administered in ischemic early phase. However, systemic HMGB1 levels reach higher concentration in ischemic delayed phase, and activate microglia resulting in brain damage. Thus, rhsTM be expected to be effective even in ischemic delayed phase. In the present study, we investigated the effects of long-term treatment with rhsTM on ischemic brain damage induced by high systemic HMGB1 levels and activated microglia in mice subjected to 4-h middle cerebral artery occlusion (MCAO). **Methods:** One day after MCAO, rhsTM was intraperitoneally administered at a dose of 1.0 or 5.0 mg/kg once a day for 7 days. Neurological score and motor coordination were measured 1 and 7 days after MCAO. HMGB1 levels were measured 1, 3 and 7 days after MCAO by enzyme-linked immune sorbent assay (ELISA). Activated microglia was evaluated 7 days after MCAO by immunostaining and Western blotting. **Results:** Systemic HMGB1 levels increased 1 to 7 days after MCAO and were higher at 7 days compared with day 1. At the same time, survival rate decreased, and expression of activated microglia increased in infarct area. Treatment with rhsTM for 7 days improved neurological score, motor coordination and survival in a dose-dependent manner. rhsTM also decreased systemic HMGB1 levels and expression of activated microglia. Moreover, treatment with rhsTM prevented the brain atrophy after cerebral ischemia. **Conclusion:** These results indicated that rhsTM improved ischemic brain damage such as survival, motor dysfunction and cerebral atrophy via inhibiting HMGB1 upregulation and microglial activation in ischemic delayed phase. rhsTM may become an effective therapeutic option against cerebral ischemia not only in the early phase but also in the delayed phase.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Title: Relationship between serum levels of BDNF and cognitive function in stroke patients

Authors: *W. CHANG, J. LEE, A. LEE, H. KIM, Y.-H. KIM
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Abstract: Introduction: Brain-derived neurotrophic factor (BDNF) is involved in neuronal survival, learning and memory, and neuroplasticity in the damaged brain. Although serum BDNF could be used as a biomarker in major depressive disorder, there was a lack of reports for serum BDNF in stroke rehabilitation. In this study, we aimed to investigate the potential of BDNF as biomarker in stroke rehabilitation for cognitive function in subacute stroke patients. **Methods:** Forty-five subacute stroke patients (mean age 62.8 yrs) were recruited in this study. All participants took the standard rehabilitation program (SRP) with daily 3-hours of rehabilitation therapy, 5 days a week, for 2 weeks. We measured the serum BDNF, proBDNF and MMP-9 at T0 (before SRP), T1 (1 week after SRP) and T2 (2 weeks after SRP). In addition, all participants were assessed with K-MMSE for cognitive function and geriatric depression scale-short form (GDS-SF) for depressive mood at three time points. Pearson correlation analysis was performed to determine the relationship between serum BDNF and each function. **Results:** Each cognitive function and depressive mood showed significantly improvement during the standard rehabilitation program for 2 weeks ($p < 0.05$). There was no significant relationship between serum BDNF and K-MMSE, However, the change of K-MMSE from T1 to T2 was significantly correlated with serum proBDNF level at T1 ($p < 0.05$). GDS at T1 was significantly correlated with serum BDNF ($p < 0.05$). In addition, the improvement of GDS from T0 to T2 tended to be correlation with serum BDNF at T0 without statistical significance. **Conclusion:** These results might suggest serum BDNF could be used as biomarker for depressive mood in subacute stroke patients. In addition, serum proBDNF might be regarded as the precursor of cognitive function improvement in subacute stroke patients. However, further study with larger participants should be needed to clarify these results.

Disclosures: W. Chang: None. J. Lee: None. A. Lee: None. H. Kim: None. Y. Kim: None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.12/Z14

Topic: C.09.Stroke

Support: AHA Predoctoral Grant
RO1 NS092455

Title: Lung-derived superoxide dismutase 3 reduces cerebral ischemia-reperfusion injury

Authors: ***K. J. GATES**, N. MAI, L. PRIFTI, S. KNOWLDEN, M. W. HALTERMAN
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Abstract: Ischemia-reperfusion injury (IRI) following acute ischemic stroke is a pervasive health problem that significantly contributes to death and disability. With the expanded use of thrombolytics and mechanical clot retrieval devices to recanalize large vessel occlusions, finding effective piggy-back therapies to address IRI-related injury remains a priority. While immunological crosstalk between the central nervous system and the periphery has been described in stroke and other acute CNS injuries, the specific signals involved and the specific role of innate immune priming on delayed neuroinflammation and post-ischemic neurodegeneration remain unclear.

Our lab recently showed that lung-brain coupling plays an essential role in the pathology of delayed CNS damage in a mouse model of global cerebral ischemia. Unlike other peripheral organs, the lung receives 100% of cardiac output, placing it in prime position to modulate systemic immune signaling. It is thought that the production of antioxidant extracellular superoxide dismutase 3 (SOD3) in the lung modulates systemic immune activation in part via effects on neutrophil priming. And while global overexpression of SOD3 has been shown to protect against hindlimb and renal ischemia-reperfusion injury, the extent to which focal manipulation of SOD3 in the lung influences neurological outcomes following cerebral ischemia remains to be seen.

In the current project, we focus on the role of lung-brain coupling in the context of transient focal stroke. Using mice that express the human transgene SOD3 in lung type II epithelial cells, we investigated the effects of manipulating the lung redox environment on neurological outcomes following transient focal stroke. Compared to wild-type (WT) littermates, TgSOD3 mice subjected to 30 minutes transient focal middle cerebral artery occlusion exhibit reduced stroke volumes (WT: $7.745 \pm 0.9255 \text{ mm}^3$ vs TgSOD3: $4.461 \pm 1.036 \text{ mm}^3$; $p < 0.005$) by 24 hours post-reperfusion. Additionally, we found that only WT mice showed a significant increase in Iba1+ cells within the infarct compared to sham controls (WT_{sham}: $7.475 \pm 0.886 \text{ cells/cm}^2$ vs WT_{MCAO}: $10.990 \pm 2.329 \text{ cells/cm}^2$; $p < 0.05$); this effect was not seen in TgSOD3 mice (TgSOD3_{sham}: $7.652 \pm 0.976 \text{ cells/cm}^2$ vs TgSOD3_{MCAO}: $9.079 \pm 1.29 \text{ cells/cm}^2$; n.s.). These findings suggest that the lung redox environment modulates CNS ischemia-reperfusion injury and argue that treatments focused on supporting an anti-inflammatory bias in the lung may represent a tractable target for ischemic stroke.

Disclosures: **K.J. Gates:** None. **N. Mai:** None. **L. Prifti:** None. **S. Knowlden:** None. **M.W. Halterman:** None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.13/Z15

Topic: C.09.Stroke

Support: UTHealth Start-up Funds

Title: Preventing microthrombi formation attenuates deficits after subarachnoid hemorrhage in mice

Authors: *D. W. MCBRIDE, P. KUMAR T., K. MATSUMURA, S. L. BLACKBURN
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Abstract: Objective and rationale - Microthrombosis has been suggested as a major factor contributing to delayed neurological deterioration in patients after subarachnoid hemorrhage (SAH). Autopsy studies in humans have found microthrombi throughout the brain parenchyma in SAH patients. However, only a few experimental studies have studied microthrombosis after SAH, and none have targeted platelet activation as a therapy. Our hypothesis is that inhibiting platelet aggregation will attenuate microthrombi following SAH in mice, reducing neurological deficits.

Methods - Subarachnoid hemorrhage was induced in 4 month old male mice via endovascular perforation or autologous blood injection into the prechiasmatic space. Mice were randomly assigned into 6 groups (n=8/group): Sham (perforation or injection), SAH (perforation or injection) + saline, and SAH (perforation or injection) + abciximab. Platelet aggregation was attenuated using the GP IIb/IIIa antagonist (abciximab) administered IV (100 mg/kg). Neurobehavior was performed on days 1-3, 5, and 7 post-SAH using a composite neuroscore and the forelimb placement test. One cohort of animals was sacrificed 2 days post-SAH, and the other at 7 days post-SAH. Microthrombi count was performed using serial sections of brains stained for fibrinogen, blood vessels (vWF or DiI), and platelets. Neurobehavioral testing performed and all data was analyzed by blinded investigating. In this exploratory study, sex differences were not examined.

Results - Mice subjected to SAH performed significantly worse in neurobehavior tests compared to Sham animals. Attenuating platelet aggregation is expected to lead to improved neurobehavioral performance. Microthrombi count are higher on days 2 and 7 post-SAH in injured mice compared to Sham. Preventing platelet activation is expected to reduce the number of microthrombi found throughout the brain after SAH.

Conclusions - The expected conclusions are that preventing platelet aggregation after SAH attenuates the formation of microthrombi, thereby reducing functional deficits.

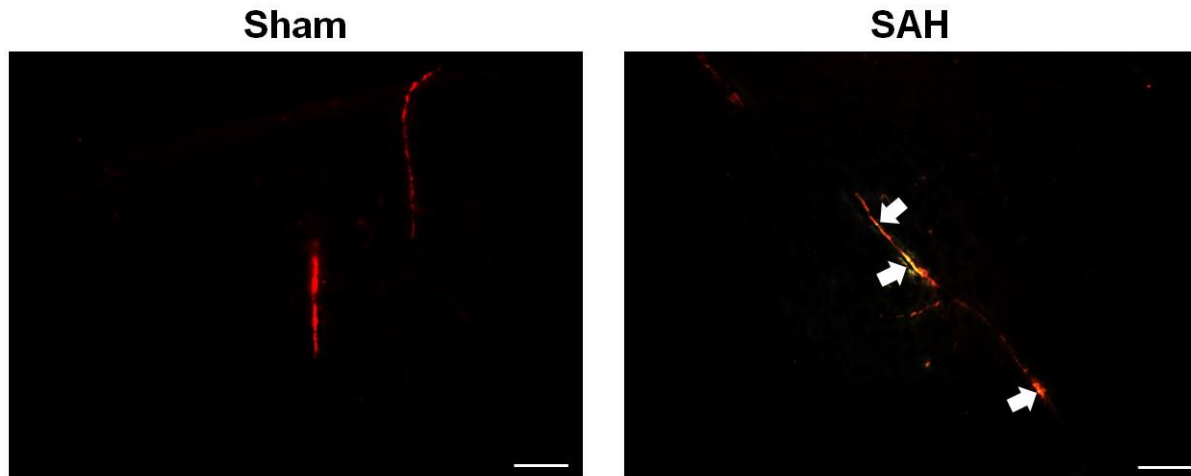


Figure 1. Microvessels stained for microthrombi 2 days post-SAH. 30 μm thick brain slice after sham surgery (left) and SAH (right) stained for vWF (red) and platelets (CD41, green). Arrows indicate platelet aggregates (yellow). Scale bar: 100 μm .

Disclosures: D.W. McBride: None. P. Kumar T.: None. K. Matsumura: None. S.L. Blackburn: None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.14/Z16

Topic: C.09.Stroke

Support: NINDS R01 NS085019

Title: Assessment of the effect of a pro-growth extracellular matrix protein, matrilin-2, on axonal sprouting in the post-stroke brain

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Abstract: Ischemic brain injuries such as stroke lead to lasting disabilities, primarily due to limited regenerative processes. Changes in the extracellular matrix of the post-stroke brain have long been speculated as a primary cause for limited recovery, with the majority of focus being placed on a growth inhibitory environment following CNS insult. Transcriptional profiling of spontaneously sprouting neurons after stroke have identified numerous extracellular matrix proteins that are differentially regulated, of which matrilin-2 shows one of the most significant changes. Matrilin-2 is an ECM adaptor protein that has been shown to be important in peripheral nerve regeneration. Previous data from this lab has identified matrilin-2 as a promoter of cortical

neuron neurite outgrowth in both control and growth-inhibitory environments. To assess its effect on axonal sprouting in the post-stroke brain, matrilin-2 was overexpressed via lentivirus in the peri-infarct cortex following a focal stroke in motor cortex. Using a quantitative cortical mapping approach, we show differential responses in axonal sprouting from neurons that overexpress matrilin-2 compared to neurons that do not overexpress matrilin-2 from the same cortical region. Our results begin to explore how a pro-regenerative environment can enhance functional recovery in the post-stroke brain.

Disclosures: **S.P. Bridges:** None. **M. Machnicki:** None. **S.T. Carmichael:** None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Program #/Poster #: 054.15/Z17

Topic: C.09.Stroke

Support: NIH Grant NS085272

Title: The acute peripheral immune response in stroke-affected skeletal muscle

Authors: ***M. BALCH**^{1,2}, H. HARRIS¹, S. GNYAWALI¹, S. KHANNA¹, C. K. SEN¹, C. L. RINK¹

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Abstract: While skeletal muscle is critically affected by stroke injury and is a key contributor to disability in stroke patients, less than 3 percent of ischemic stroke literature in the past decade has focused on skeletal muscle effects. The canonical inflammatory reaction to traumatic skeletal muscle injury is well-defined and includes early neutrophil infiltration, followed by pro-inflammatory M1 macrophages that later shift to an anti-inflammatory M2 phenotype. Non-canonical recruitment patterns have been observed in other neuromuscular disorders, but the impact on stroke-affected skeletal muscle is not well studied. Here, we leverage a software-controlled Robot-Assisted Mechanical Therapy device (RAMT) to reproducibly deliver post-stroke physiotherapy and study the skeletal muscle immune response to stroke injury and physical therapy.

Male Wistar rats (N=26) were subjected to transient middle cerebral artery occlusion, followed by either RAMT treatment on the stroke-affected hindlimb (30 minutes daily under anesthesia; 0.5N force, 1Hz frequency, 10mm linear path) or no treatment (anesthesia only) beginning post-stroke day (PSD) 1 and continuing up to PSD7. Hindlimb skeletal muscle was collected from stroke-affected and contralateral limbs, and immunohistochemistry was used to characterize post-stroke inflammatory cell populations.

At PSD3, RAMT induced significantly higher neutrophil counts in both stroke-affected and contralateral hindlimb skeletal muscle -- three-fold higher than that of untreated controls. Notably, at this time point there was no appreciable recruitment of M1 macrophages or differences in M2 macrophage numbers between control and RAMT-treated animals. At PSD7, however, untreated controls experienced a significant loss of M2 macrophages in skeletal muscle; RAMT treatment protected against this loss. Concomitant with this protection, RAMT upregulated expression of anti-inflammatory IL-1ra at PSD7. Furthermore, a query of the miRNA transcriptome at PSD3 and PSD7 uncovered differential expression of miRNAs in skeletal muscle known to regulate inflammation and immune cells.

Taken together, RAMT serves as a valuable tool to assess effects of stroke injury and physical therapy at the skeletal muscle level. A small but growing body of literature has identified acute peripheral organ system responses to central nervous system injury. This work seeks to characterize the acute effects of ischemic stroke on skeletal muscle. Understanding the stroke-induced immune cell response in skeletal muscle will further inform therapy guidelines and advance neurophysiological rehabilitation treatment of stroke.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

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Program #/Poster #: 054.16/Z18

Topic: C.09.Stroke

Support: National Institutes of Health grant 9R01NS090904 to BVZ

Title: Multi-parametric MRI approach demonstrates protective effects of 3K3A-activated protein C in a novel model of white matter stroke

Authors: *M. T. HUUSKONEN¹, Y. WANG¹, A. MONTAGNE¹, Z. ZHAO¹, J. H. GRIFFIN², B. V. ZLOKOVIC¹

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Abstract: Activated protein C (APC) is a blood protease with anticoagulant and cell signaling activities mediated by protease activated receptors (PAR 1 and 3). 3K3A-APC is a recombinant variant of APC with reduced anticoagulant activity and retained PAR activation potential. This favorable combination of reduced bleeding risk and neuroprotective properties have been demonstrated in multiple animal models of brain diseases (including but not limited to ischemic stroke, traumatic brain injury and amyotrophic lateral sclerosis) and has led to the entrance of

3K3A-APC into clinical trials as a treatment for acute ischemic stroke. Here, we used an advanced multi-parametric MRI approach to study the protective effects of 3K3A-APC in a mouse model of induced white matter stroke. The MRI scans were performed using 7T PET/MRI scanner (MR Solutions) and a standard quadrature coil 1 and 7 days after the stroke. The protocol consisted of T2-weighted anatomical sequence (FSE), T1 (FLASH) and T2 (MEMS) mapping, EPI-DTI and gadolinium-enhanced DCE-MRI (FLASH). Parametric maps were acquired using Rocketship software. With the protocol used we were able to detect the small focal white matter damage induced by the stereotaxic injection of vasoconstrictor N^5 -(1-Iminoethyl)-L-ornithine (L-NIO). In addition, 3K3A-APC was able to reduce the lesion size detected by T2-weighted imaging and prevent the damage on white matter tracts based on EPI-DTI. Moreover, 3K3A-APC normalized alterations in apparent diffusion coefficient and T2-relaxivity induced by white matter ischemia. Finally, 3K3A-APC treated animals had smaller BBB permeability at the lesion site based on lower K_{trans} values. In conclusion, MRI is a suitable method to follow the progression of white matter stroke in mice and revealed the protective effect 3K3A-APC in this model.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Support: National Research Foundation of Korea (NRF) grant, NRF-2017R1A2A1A05000730
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Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, HI17C1501

Title: Different brain connectivity changes and responsiveness to dual-mode noninvasive brain stimulation over bilateral primary motor cortices in stroke patients

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Abstract: Noninvasive brain stimulation (NBS) such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) has recently been applied to stroke patients with motor impairment. NBS is helpful for motor function restoration by modulating the cortical excitability of stroke patients. It is well known that there is a significant inter-individual variability in efficacy of NBS, however, the underlying neural mechanism of this variability was not sufficiently investigated. In this study, we investigated the motor network connectivity changes in patients receiving NBS over their bilateral primary motor cortices and compare their responsiveness to NBS and subsequent network connectivity changes. Twenty-one subacute stroke patients (13 males, mean age 59.6 ± 11.5 yrs) participated. NBS was applied using both rTMS and tDCS over bilateral primary motor cortices (M1s); simultaneous application of 2 mA anodal tDCS over the ipsilesional M1 and 1,000 pulses of 1 Hz rTMS at 90 % resting motor threshold over the contralesional M1 for 20 minutes. All participants underwent 10 daily NBS sessions for consecutive 2 weeks. Participants were classified into two groups (good and poor responder groups) according to their responsiveness to NBS measured by improvement of Fugl-Meyer Assessment Upper Extremity (FMA-UE) score; good responder group (FMA-UE gain ≥ 10 ; 7 males and 5 females, mean age 58.8 ± 13.1 yrs) and poor responder group (FMA-UE gain < 10 ; 6 males and 3 females, mean age 60.6 ± 11.3 yrs). Two times of resting-state functional MRI were obtained before and after NBS and alterations in the motor network connectivity were analyzed using MATLAB (Mathworks, Inc.). M1 intrahemispheric connectivity, interhemispheric connectivity, and global network efficiency were analyzed to investigate differences in the motor network characteristics between good and poor responders. There were significant differences in motor network connectivity between good and poor responders. Specifically, the M1 intrahemispheric connectivity in good responders noticeably showed the imbalance between affected and unaffected connectivity prior to NBS which was drastically restored after NBS. In addition, interhemispheric connectivity and motor network efficiency tended to be greater in good responders than poor responders. These results may indicate that NBS gives more benefit to the patients who suffer from existing imbalance of motor network connectivity caused by stroke, which can provide insight into patient-specific NBS treatment according to the brain network characteristics prior to stimulation.

Disclosures: J. Lee: None. A. Lee: None. H. Kim: None. K. Kim: None. W. Chang: None. Y. Kim: None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

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Program #/Poster #: 054.18/AA2

Topic: C.09.Stroke

Support: Japan Agency for Medical Research and Development

Title: Relationship between EEG during motor imagery and upper limb function after the intervention with KiNvis and EEG-based BCI in patients with severe upper limb paralysis after stroke

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Abstract: [Introduction]Previous studies demonstrated independently that kinesthetic illusion induced by visual stimulus (KiNvis) and electroencephalogram (EEG)-based brain-computer interface (BCI) could possibly improve motor function in patients with severe upper limb hemiplegia due to stroke. The aim of the present study was to investigate brain activity changes as measured with EEG during motor imagery (event-related desynchronization: ERD) before and after the intervention with KiNvis and BCI. [Methods]Thirteen patients with severe upper limb paralysis after stroke (5 with right and 8 with left hemiplegia) participated. All patients scored 1a for finger movement (no finger extension) as assessed with Stroke Impairment Assessment Set. The experimental protocol was conducted in accordance with the Helsinki Declaration and was approved by the ethical committee of Shonan Keiiku Hospital. The experiment consisted of 10 days intervention on weekdays (KiNvis and BCI) and evaluations before and after the intervention. During KiNvis therapy, pre-recorded movie was projected on the monitor which was set over the forearm so that the position of the display would give an illusion that the patient's forearm was actually the same as that depicted in the movie. The movie showed grasping and opening of the uninvolved hand, and was repeatedly played for 20 min. EEG, Fugl-Meyer Assessment (FMA) and modified Ashworth Scale (MAS) were assessed. EEG was recorded from C3/4, CP3/4 and P3/4. ERD was selected as the most reactive frequency band from alpha-band and beta-band on each channel. A Wilcoxon signed-rank test was performed to compare ERD, FMA and MAS between before and after the interventions. Correlations between ERD and FMA or MAS were calculated with Spearman's rank correlation. [Results]The beta-band ERD of P3/4 recorded from the damaged hemisphere significantly decreased after the intervention compared to pre-intervention ($p=0.046$). Upper limb FMA significantly improved after the intervention ($p=0.002$). MAS of finger flexor muscles significantly decreased after the intervention ($p=0.002$). Although no significant correlation existed between the beta-band ERD of P3/4 in the damaged hemisphere and MAS of flexor muscles before the intervention, a significant positive correlation was observed after the intervention (before; $r=0.091$, $p=0.767$, after; $r=0.730$, $p=0.005$). [Conclusions] In the present study, spasticity in the flexor muscles decreased with the reduction of the beta-band ERD at P 3/4 in the damaged hemisphere. A linear relationship between those two variables after the intervention was shown.

Disclosures: **M. Okawada:** A. Employment/Salary (full or part-time); Keio University, Shonan Keiiku Hospital. **F. Kaneko:** A. Employment/Salary (full or part-time); Keio University, Shonan Keiiku Hospital. 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.; Joan Agency for Medical Research and Development. **K. Shindo:** A. Employment/Salary (full or part-time);; Shonan Keiiku Hospital. **M. Yoneta:** A. Employment/Salary (full or part-time);; Keio University, Shonan Keiiku Hospital. **K. Akaboshi:** A. Employment/Salary (full or part-time);; Shonan Keiiku Hospital. **M. Liu:** A. Employment/Salary (full or part-time);; Keio University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Japan Agency for Medical Research and Development.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.19/AA3

Topic: C.09.Stroke

Support: NIH Grant R01HD053793

Title: The Fugl-Meyer scale does not capture recovery of motor control following stroke

Authors: ***A. M. HADJIOSIF**¹, M. BRANSCHIEDT^{2,4}, M. A. ANAYA², K. D. RUNNALLS², J. KELLER⁵, A. J. BASTIAN^{3,5}, P. A. CELNIK², J. W. KRAKAUER¹

¹Neurology, Neurosci., ²Physical Med. and Rehabil., ³Neurosci., Johns Hopkins Univ., Baltimore, MD; ⁴Neurol., Univ. of Zurich, Zurich, Switzerland; ⁵Kennedy Krieger Inst., Baltimore, MD

Abstract: The most commonly used scale for motor impairment after stroke is the Fugl-Meyer Stroke Scale (FM), which mainly examines the ability of patients to perform predefined movements outside of pathological synergies, with many of these movements requiring the patient to support the weight of the arm. Since reductions in impairment would translate to improvements in motor control, the FM has in turn been assumed to also capture the quality of motor control. However, the scale rates overall success in performing each movement, without assessing the quality of execution. In addition, recent work has shown that motor control is improved with weight support (Sukal et al., 2007), suggesting that recovery of strength rather than control per se could drive improvements in the FM. Moreover, improvements in FM vs. improvements in motor control have been shown to occur at different rates after stroke, casting doubt on a one-to-one correspondence (Cortes et al., 2017). Thus, while improvements in FM would generally reflect improved motor control, the exact relationship between these two and how they interact during recovery remains poorly understood.

Here, we investigate the relationship between reaching kinematics and upper limb FM scores for patients during the acute (<2 mo. post stroke, N = 15) vs. chronic (>6mo. post stroke, N = 20) stroke phases. Participants performed 10cm point-to-point reaching movements to 8 different

targets on a 2D plane with arm support. We evaluated the reaches of stroke patients using functional principal component analysis (fPCA), a method which compares patients' movement trajectories to those of a control population (N = 7). Specifically, we calculated the average squared Mahalanobis distance (AMD²) between each patient's reaches and the control population (Cortes et al., 2017).

Unsurprisingly, we found that stroke patients displayed impaired kinematics compared to controls, with this impairment generally increasing with decreasing FM. Interestingly, however, acute patients showed markedly worse kinematics than chronic patients with similar or higher FM scores. This finding suggests that the FM scale - a canonical tool for measuring neurological impairment after stroke - does not fully capture the underlying changes in motor control between the acute and chronic stage: in the latter stage, patients can have better kinematic performance for worse FM scores. This raises interesting questions about the degree to which strength-focused impairment scales such as FM reflect the full spectrum of neurological impairment or whether a fuller picture of impairment may be provided by additionally considering measures of kinematic performance.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.20/AA4

Topic: C.09.Stroke

Title: Efficient engraftment of mesenchymal stem cells in a rat chronic stroke model

Authors: ***D. JO**, G.-H. KIM, D.-Y. CHANG, J. YOON, S.-S. KIM, H. SUH-KIM
Anat., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: Mesenchymal stem cells (MSCs) have been reported to improve the recovery from ischemic stroke. However, MSCs have not been recognized clinically because their therapeutic effects were not demonstrated clearly, especially in chronic stroke patients. Moreover, routes and procedures for transplantation of MSCs have not been established. In our previous study, we showed that the transplantation of neurally-induced MSCs by introducing Neurogenin1 (MSC/Ngn1) dramatically improved the stroke outcome compared to the parental MSCs in an acute stroke model. In this study, we investigated whether other types of MSC cells were advantageous in a chronic stroke model compared to the parental MSCs. We also developed a transplantation procedure, which was less invasive than the intracranial injection while allowing an efficient engraftment of transplanted cells. We will discuss the results on how to facilitate the

engraftment of transplanted cells toward the infarcted area in a chronic stroke model. We propose that as a pre-clinical evidence, our results can be extended to the future clinical field to administer functionally enhanced stem cells to the chronic stroke patients.

Disclosures: **D. Jo:** None. **G. Kim:** None. **D. Chang:** None. **J. Yoon:** None. **S. Kim:** None. **H. Suh-Kim:** None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

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Program #/Poster #: 054.21/AA5

Topic: C.09.Stroke

Support: Department of Biotechnology, Govt. of India

Title: Monomethyl fumarate mediates neuroprotection against ischemia reperfusion injury in rats via activating endogenous antioxidant (nrf2/ho1) pathway

Authors: ***D. SINGH**¹, R. KH², U. SHARMA³, J. NR³, A. DINDA⁴, Y. GUPTA²

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Abstract: Stroke represents one of the major causes of mortality and morbidity worldwide. Stroke pathophysiology has been explored successfully in last few decades; however tPA remains to be the only treatment option with limitations. Increasing number of evidences suggest that activating endogenous antioxidant pathway by stimulation of nuclear factor erythroid-2-related factor 2 (Nrf2) can play a key role in cellular defense against oxidative stress in ischemic penumbra. This study was performed to test the mechanism of neuro-protective effect of monomethyl fumarate (MMF). In male Sprague Dawley rats (270±20 g), middle cerebral artery were occluded for 90 min. Occlusion was confirmed by Laser Doppler flow meter. MMF (20 mg/kg) was administered in two divided doses at 30 min post ischemia and 5 min post reperfusion. After 24 hours, neurobehavioral parameters were assessed followed by T2 imaging using 7.0T animal MRI to assess effect on infarct. For Nrf2 and HO-1 expression, rats were euthanized and cytoplasmic/nuclear fractions were separated. Cytoplasmic fraction was used to assess HO-1 expression whereas Nrf2 expression was checked in nuclear fraction by western blot. For immunofluorescence analysis, rats were perfused with paraformaldehyde, cryo-sections were stained with Nrf2, HO1, NeuN and GFAP followed by counterstaining with DAPI. Post occlusion, cerebral blood flow was reduced by 80.2 ± 2.9% of baseline and post reperfusion 70.4 ± 4.1% of blood flow was restored. MMF treatment significantly (p<0.05) improved neurobehavioral parameters and cerebral infarct when compared to MCAo group. Expression of nuclear Nrf2 and cytoplasmic HO1 were increased significantly (p<0.05) in peri-infarct cortex

after treatment with MMF. Immunofluorescence study revealed increased expression of Nrf2 in neurons and HO1 in neuron as well as astrocytes in peri-infarct region of MMF group. Our results indicate the neuro-protective potential of MMF in peri-infarct cortex after ischemia reperfusion injury by activation of Nrf2/HO1 pathway.

Disclosures: **D. Singh:** None. **R. Kh:** None. **U. Sharma:** None. **J. Nr:** None. **A. Dinda:** None. **Y. Gupta:** None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.22/AA6

Topic: C.09.Stroke

Support: National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT) , 2017R1C1B5076731

Title: An evaluation gap between patients and clinicians in left hemiparesis and right hemiparesis

Authors: **S. CHOI**, ***S. KIM**
Jeonju Univ., Jeonju, Korea, Republic of

Abstract: The aim of this study is to compare the performance evaluation by patients with stroke (left hemiparesis and right hemiparesis) and to the performance evaluation by clinicians in experimental tasks including use of upper extremity during activity of daily living. In addition, the relationship between clinician's evaluation, patient's evaluation, and patient's performance predictions is examined. Total forty individuals with subacute to chronic stroke are recruited and twenty subjects have left-hemisphere stroke damage (LHD) and the other twenty have right-hemisphere stroke damage (RHD). The experiments are conducted for two-days with one week of interval between days and Actual amount of use test (AAUT) is performed to measure clinician's evaluation, patient's evaluation, and patient's performance predictions. Difference between LHD and RHD in evaluation gap, which is a difference between clinician's and patient's evaluation of performance, will be analyzed using mixed-effect linear regression model with group as a fixed factor and each individual as a random factor. The correlation coefficients among clinician's evaluation, patient's evaluation, and patient's performance predictions will be calculated using either Pearson or Spearman method depending on the distribution of data. We plan to show the results of the difference between LHD and RHD in the evaluation gap: LHD underestimates while RHD overestimates their performance in AAUT score in comparison to clinician's ratings. Furthermore, the correlation between clinician's evaluation and patient's performance prediction will be presented by each stroke group. An evaluation gap between

patients with subacute to chronic stroke and clinicians seems to be related to actual use of the more-affected arm in activities of daily livings. Once the individuals with stroke underestimate their capability to use their more-affected arms, this may potentially lead to the less use of their more-affected arms.

Disclosures: S. Choi: None. S. Kim: None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.23/AA7

Topic: C.09.Stroke

Support: NIH grants NS085568 (LW/SPY)
VA National Merit grant RX000666 and RX001473 (SPY)

Title: Acute treatment of hypothermic compounds attenuates psychological deficits chronically developed in the mice model of focal ischemic stroke

Authors: *W. ZHONG¹, Y. YUAN¹, X. GU¹, C. QU¹, S. KIM¹, M. LOYE², T. DIX³, L. WEI¹, S. YU¹

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Abstract: Stroke is one of the leading causes of death in the world. Up to 2/3 of survivors suffer from functional disabilities and about 40% of patients develop psychological/psychiatric liabilities, such as post-stroke depressive (PSD), and occasionally cognitive deficits. Basic and translational research on PSD after stroke, especially on small stroke models, is limited. Antidepressants are common clinical treatments for PSD; their efficacies, however, are far from satisfactory. Emerging evidence from pre-clinical and clinical studies has shown that therapeutic hypothermia is a promising acute protective therapy after strokes; meanwhile, its effect on post-stroke psychological symptoms has rarely been examined. We have developed a pharmacological hypothermia treatment using neurotensin receptor 1 agonists and demonstrated brain protective effects against stroke and TBI. In the present investigation, we inspected the potential antagonism of acute post-stroke treatment using the hypothermic drug HPI363 to treat chronically developed psychological disorders in a mice model of focal ischemic stroke in the right sensorimotor cortex. Stroke animals showed sensorimotor functional deficits several days after stroke and underwent spontaneous recovery in the adhesive removal test and corner test 2-4 weeks later. However, in a series of behavioral examinations, such as the force swim, tail suspension, sucrose preference, open field and water maze tests, these animals gradually developed depressive/anxious behaviors and cognitive deficits 4 weeks after stroke. The

symptoms continued to deteriorate until 8 weeks post-stroke at the end of experiments. In PCR and Western blot assessments, the expression levels of oxytocin and BDNF were significantly reduced in the prefrontal cortex (PFC), which are associated with the psychological regulation and consistent with the behavioral observations. In stroke mice that received 6-hrs hypothermic treatment of HPI363 acutely after stroke, the development of depressive and anxious behaviors, and cognitive dysfunctions were noticeably attenuated 6 weeks after stroke. Our data suggest that an acute post-stroke treatment with the neurotensin receptor 1 agonist has a delayed benefit of attenuating chronically developed post-stroke psychological disorders. The mechanisms underlying the prolonged effect are under investigation.

Disclosures: **W. Zhong:** None. **Y. Yuan:** None. **X. Gu:** None. **C. Qu:** None. **S. Kim:** None. **M. Loye:** None. **T. Dix:** None. **L. Wei:** None. **S. Yu:** None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.24/AA8

Topic: C.09.Stroke

Title: Determining translational magnetic resonance imaging parameters predictive of therapeutic efficacy in a porcine ischemic stroke model

Authors: ***S. E. SPELLICY**^{1,3}, E. E. KAISER^{1,2}, M. M. BOWLER¹, B. J. JURGIELEWICZ¹, R. L. WEBB⁴, F. D. WEST², S. L. STICE²

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Abstract: To bridge the gap between the bench and the bedside, we have developed a porcine middle cerebral artery occlusion (MCAO) ischemic stroke model. Due to similarities to humans in brain size, gyrencephalacy, and white matter content, this porcine model has the potential to enhance translation of therapeutics over more traditional rodent models. Our objective was to develop a multiparametric analysis approach to identify clinically relevant MRI parameters predictive of long-term motor and behavioral outcomes in the porcine model and assess the potential of these parameters to predict the efficacy of our novel treatment, neural stem cell-derived extracellular vesicles (NSCEV). To induce a stroke, a permanent right-sided MCAO was performed on 16 male landrace pigs, which were subsequently divided into either treatment or sham group. NSCEV or PBS was administered at 2, 14, and 24 hours, and MR Imaging was conducted at day 1 and 84 post stroke induction. Data on 65 gait and 25 behavior parameters was collected pre-stroke, and over 84 days following MCAO. We then ran pairwise correlations of these parameters against 19 structural MRI parameters for each group and day tested. We found that out of all measured MRI parameters, coronal and axial midline shift (MLS), measured at 24-

hour post stroke, had the highest number of significant (<0.01) correlations to gait and behavior parameters out to 84 days post-MCAO. These early 24-hour MLS measurements were even more predictive of gait and behavior parameters at day 84 than resultant chronic MLS measurements conducted at day 84 post-MCAO. When assessing the treatment effect of NSCEV on axial and coronal MLS there was a significant difference in mortality between the groups of animals with high MLS ($>2.2\text{mm}$) compared to low MLS ($<2.2\text{mm}$). In animals with high MLS, NSCEV-treated animals had 100% survival, while sham animals had only 25% survival. Modified Rankin scores (mRS) of NSCEV-treated animals decreased at comparable rates in animals with high and low MLS, whereas high MLS sham animals had a significantly (<0.05) slower decrease in mRS scores, and therefore recovery, by 1-week post MCAO. Using multiparameter correlation analysis, we identified midline shift as a predictive MRI parameter in the porcine MCAO model of stroke. The trends and differences between our NSCEV and sham treatment groups elucidated through midline shift in the pig model mirror human clinical data in regard to functional recovery trends and survival rates dependent on midline shift severity. Midline shift has proven to be a critical parameter in the pig model ischemic model of stroke, making this a powerful tool for further investigation of therapeutic interventions.

Disclosures: **S.E. Spellacy:** None. **E.E. Kaiser:** None. **M.M. Bowler:** None. **B.J. Jurgielewicz:** None. **R.L. Webb:** A. Employment/Salary (full or part-time);; Aruna Biomedical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aruna Biomedical. **F.D. West:** None. **S.L. Stice:** A. Employment/Salary (full or part-time);; Aruna Biomedical. 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.; Aruna Biomedical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aruna Biomedical.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.25/AA9

Topic: C.09.Stroke

Support: National Science Foundation Graduate Research Fellowship under Grant No. DGE-1256260
Rackham Graduate Student Research Grant

Title: Sensory and motor assessment of stroke patients

Authors: *Y. ACOSTA-SOJO¹, C. KRISHNAN², B. J. MARTIN¹

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Abstract: Stroke is the leading cause of long-term physical disability in the United States. Physical rehabilitation following a stroke is crucial for recovery, improving patient independence, and reducing cost for outpatient services. However, traditional and current approaches have ignored intrinsic asymmetries and rarely differentiate the specific sensory and/or motor needs after stroke. For this reason, the goal of this pilot study was to investigate the alteration of sensory information from each limb/hemisphere system in mildly to moderately affected stroke patients. The sensory systems were tested by passive proprioceptive perception of upper limb position and movement. Position sense was tested with eyes closed while participants matched a reference position imposed by a robotic arm in two different conditions: ipsilateral remembered and contralateral concurrent. Movement sense was tested with eyes closed while participants reproduced with the opposite arm the perceived movement elicited by a vibration applied to the distal tendons of the triceps muscle of the reference arm. The preliminary results were obtained from two patients whose left hemisphere was affected by a mild and moderate stroke, respectively. The results indicate a significant alteration of position and movement sense asymmetry between right and left limb systems. They vary largely between the patients; however sensory alterations are pronounced in both. A lack of consistency was observed for the patient affected by a moderate stroke and a motor deficit is likely for that patient. It is worth noting that “asymmetry exacerbation”, which does not mean greater errors, is to be considered when comparing to intrinsic asymmetries in healthy controls.

Disclosures: Y. Acosta-Sojo: None. C. Krishnan: None. B.J. Martin: None.

Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.26/AA10

Topic: C.09.Stroke

Support: NIGMS 5P20GM109098-04

Title: Analysis of risk-based decision making in rats following medial prefrontal stroke

Authors: *C. M. O'HEARN, C. WHIRTLEY, T. K. SHAVER, C. E. CABRAL, A. D. LAKE, B. ZHU, A. N. RICHMOND, C. VONDER HAAR

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Abstract: In rodents, complex cognition is controlled largely by various parts of the frontal lobe including the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC). Preclinical stroke studies have identified deficits in decision making and other cognitive processes following stroke. The rodent gambling task (RGT) is a preclinical model of the Iowa gambling task and allows for the characterization of risky decision making in rodents. Relatively few studies have examined decision making in preclinical stroke, and none have examined risky decision making using the RGT.

The current study tested 23 male Long-Evans rats on the RGT following frontal stroke or sham procedures. Rats were randomly assigned to stroke or sham groups, and given a bilateral stroke centered in the mPFC using endothelin-1 (n=13) or saline injection (n=10). One month after surgery, animals were then trained on the RGT in a standard operant chambers. Rats were presented with four choices; two were low risk (high reinforcement probability/low punishment probability) and two were high risk (low reinforcement probability/high punishment probability). Greater reinforcer magnitude was also associated with the high risk options (e.g. 4 pellets vs 1 pellet).

Frontal stroke increased risky decision making and impulsivity on the RGT. Stroke increased choice of the high-risk option and number of premature responses. By establishing the ability to assess clinically-relevant decision making in rats after stroke, future studies will be able to determine efficacy of therapeutics for complex cognitive function, an area in great need of development.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.27/AA11

Topic: C.09.Stroke

Support: NS056839

Title: Towards a reproducible rodent model of lasting upper extremity impairments after subcortical white matter infarcts

Authors: *E. NUDI¹, C. NIELSON¹, T. A. JONES²

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Abstract: Around 800,000 people in the United States are affected by stroke yearly and it is the fifth leading cause of death. Around 25% of strokes occur in small vessels that damage subcortical white matter regions and lasting disability in the upper limb is common following

these types of stroke. Research in animal models have relied heavily on motor cortical infarcts to model these impairments. Our goal is to establish a rodent model of capsular infarcts that is suitable for modeling lasting upper extremity impairments. This study aims to determine relationships between characteristics of infarcts of the posterior limb of the internal capsule (PLIC) in rats and the severity and chronicity of post-infarct forelimb motor impairments, as assayed in sensitive skilled reaching tasks. Separate cohorts of adult male Long-Evans rats were preoperatively trained on the isometric pull task (Vulintus, Mototrak) or the single pellet retrieval task. They then received subcortical white matter infarcts of PLIC induced via endothelin-1 infusions or photothrombosis, respectively. For the latter, after Rose Bengal injections via the saphenous vein, electrical stimulation-guided placement of an optrode was used to induce PLIC-localized infarcts. Rats were given a recovery period of 4-5 days followed by periodic probes on the pre-operatively trained reaching task. Overall, infarcts of either induction method resulted in an initial marked decrease in success rates in reaching performance. This was followed by relatively rapid performance improvements which were no longer significantly different from preoperative performance levels by 3-4 weeks. Thus, neither PLIC infarct induction method resulted in chronic forelimb impairments in skilled reaching, in contrast to the effects of substantial motor cortical infarcts. However, there was considerable variability in both the magnitude of initial impairments and the rate and degree of recovery within studies and across them. The endothelin-1 method resulted in highly variable infarct extents and impairment severities. The range of each was more constrained after photothrombotic infarcts, but behavioral-level variability was nonetheless notable. Ongoing work is taking advantage of the range on behavioral and infarct levels within and across studies to identify infarct characteristics linked with the greatest chronicity of impairments.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.28/BB1

Topic: C.09.Stroke

Title: Cerebrovascular disease-causing mutation, ACTA2^{R179H} disrupts the functions of α -actin in patients transdifferentiated smooth muscle cells

Authors: Y. SUBBURAJ¹, C. L. CARDENAS¹, B. GYORGY¹, D. M. MILEWICZ², M. E. LINDSAY¹, *P. L. MUSOLINO¹

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Abstract: Heterozygous missense mutation in the ACTA2 gene at Arginine 179 by substitution to histidine (R179H) produce a severe and penetrant phenotype characterized by diffuse smooth

muscle cell (SMC) dysfunction, aortic aneurysms and a form of devastating cerebrovascular disease. The involvement of brain vasculature and its onset during childhood distinguishes ACTA2^{R179H} from all other mutations and is characterized by progressive white matter injury, vasco-occlusive (moyamoya-like) vasculopathy, and ischemic strokes. Patient histological specimens and preliminary data from available mice models suggest that the progressive narrowing and occlusion of brain arteries is due to vascular SMC proliferation, a compensatory mechanism for their ineffective contractility caused by the mutant actin. As a first step towards targeted treatments we characterized dermal fibroblast and transdifferentiated SMC from ACTA2^{R179H} patients and controls using western blot, PCR and functional assays. We confirmed SMC phenotype of transdifferentiated cells by mRNA expression of other smooth muscle cell specific markers like MYH11, sm22, calponin and smoothelin. Despite higher levels of total α -actin on western blot analysis in ACTA2^{R179H} fibroblast and transdifferentiated SMC we found a decrease in fibrillary form of α -actin in the cytoplasm of ACTA2^{R179H} cells. Accordingly, ACTA2^{R179H} cells showed only a 10% increase in contractility following differentiation with TGF-B compared to 30% increase contractility in controls. ACTA2^{R179H} cells also denoted an increased proliferative/migratory behavior in wound assays. These preliminary results suggest that R179H mutation disrupts assembly of fibrillary α -SMA and alters its contractile function. Whether increased proliferation of SMC is direct consequence of the mutant actin or a compensatory mechanism for their loss in contractile capacity remains to be determined. Understanding the molecular mechanism underlying these functional phenotypes will allow us to develop and in-vitro assay where a gene-targeted approach can be tested.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.29/BB2

Topic: C.09.Stroke

Support: NIH/NINDS R01 NS081055

Title: Vessel-derived signaling factors regulate neural progenitor cell responses to cortical stroke

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Abstract: Stroke is a leading cause of adult disability, yet therapies that promote neural repair and functional recovery are limited. While stroke causes tissue damage, ischemic injury also initiates a limited endogenous repair program that includes the formation of new blood vessels and the generation of new neurons and glia. In response to stroke, neural progenitor cells in the subventricular zone proliferate and migrate to perilesional tissue. Upon their migration, stroke-responsive neural precursors localize to remodeling blood vessels, forming a neurovascular niche in which angiogenesis causally regulates neurogenesis. However, the molecular communication systems mediating vascular recruitment of neural progenitor cells are incompletely understood. Candidate vessel-derived signaling molecules were identified via whole-genome sequencing of perilesional vascular endothelial cells and neuroblasts following middle cerebral artery stroke. Candidate ligands were found to be upregulated in vascular endothelial cells while their receptors were upregulated in neuroblasts 7 days after stroke. To investigate the role of these signaling systems on post-stroke neurogenesis, lentiviral overexpression or mRNA-mediated knockdown of each candidate ligand in peri-infarct vasculature was performed. Both initial recruitment and long-term survival of stroke-responsive neural progenitors was assessed. Additionally, lineage tracing of subventricular zone-derived neural precursor cells, born at the time of stroke, was performed following ligand gain- or loss-of-function to further delineate the cell populations responding to post-stroke vascular cues. Finally, primary neural stem cells derived from adult subventricular zone were used to investigate the role of candidate receptor inhibition on neurogenesis in vitro. Together, results identify novel neurovascular signaling systems regulating neural repair after stroke, and provide insight into potential therapeutic targets that might enhance the brain's limited capacity for regeneration after stroke. Supported by NIH/NINDS R01 NS081055.

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Poster

054. Stroke, Damage, or Disease: Assessment and Treatment I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 054.30/BB3

Topic: C.09.Stroke

Support: 3R01NS053606-03S1

Title: Distributions of power variables reveal similar patterns of abnormal flexor-extensor activity across stroke survivors

Authors: *F. C. HUANG

Arms + Hands Lab., Shirley Ryan Abilitylab, Chicago, IL

Abstract: This study evaluated whether distribution analysis of motor exploration, or self-directed practice in arm movement, could reveal common features of abnormal flexion-extension in stroke survivors. In previous studies (Wright, Patton, and Huang, 2018; Huang and Patton, 2016), stroke survivors (n=22) and neurally intact individuals (n=10) were asked to perform motor exploration during planar arm motion in the absence of external loads. We instructed participants to move at a variety of speeds and directions, while trying not to repeat the same movements. We hypothesized that stroke survivors would exhibit stereotypical patterns of flexor synergy, manifesting as over-expression of flexion of the elbow. In particular, we expected distributions of acceleration to exhibit biases depending on the direction of motion. Combining data from our previous studies, we computed histograms of the power variables, the velocity and acceleration, of hand endpoint motion in the sagittal plane. To visualize the impact of motor deficits, we examined how the distributions of power variables for stroke survivors differed with respect to the average distribution of the neurally intact group. Intriguingly, these plots revealed for participants exhibited similar patterns of uneven distributions in terms of flexion-extension behaviors. We also observed a few cases of over-expression of extreme low and high magnitude states for stroke survivors, which suggests abnormal velocity-dependent behaviors. To quantify these effects, we defined a metric, the Extension Bias, as the difference in mean value of acceleration during extension versus that of flexion. We computed a separate Extension Bias for the case of braking (deceleration while extending the arm), versus driving (acceleration while extending the arm). Our main finding was that stroke survivors exhibited an average bias of 0.12 m/s^2 (CI: 0.0321, 0.2081) towards extension for braking, while healthy group exhibited the opposite trend -0.2255 m/s^2 (CI: -0.4620, 0.0109). The group differences in extension bias for braking was significant ($p = 8.8960e-04$). In addition, we found that in terms of driving movement, both groups exhibited a positive extension bias (mean 0.1089 m/s^2 , CI: 0.0323, 0.1855). However, stroke survivors still showed less overall driving ($p = 0.0044$). These findings offer the exciting prospect that flexor synergies manifest from over-expression of braking during extension as opposed to excessive flexor activity. Our methods could be used to refine the design of robot-assisted therapies to specifically target abnormal flexion-extension behaviors in stroke survivors.

Disclosures: F.C. Huang: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.01/BB4

Topic: C.09.Stroke

Support: TOYOTA MOTOR CORPORATION

Title: Flexible brain networks during stroke recovery

Authors: *Y. O. OKAZAKI¹, N. HATTORI^{2,1,3,4}, T. KAWANO^{2,1,3}, M. HATAKENAKA², I. MIYAI², K. KITAJO¹

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Abstract: The human brain can adapt to the environment due to dynamic characteristics of the functional architecture in the brain networks, even when it lapses into a seriously damaged state. In former clinical studies, the reorganization of brain networks, via the recruitment of substitutable networks, relates to recovery after stroke. Based on this notion, recovery from a stroke must depend on whether the brain is flexible enough to change the network. To test this hypothesis, we examined the flexibility of the network, which measures the temporal change of the nodal composition within the community, during stroke recovery.

Twelve stroke patients (mean±sd age, 67±15) with right cortical/subcortical hemispheric lesions underwent electroencephalography (EEG) recordings and behavioral tests (Fugl-Meyer Assessment: FMA for motor impairment and Functional Independence Measure: FIM for functional outcome) at 40±10 days (early sub-acute phase) and 167±41 days (late sub-acute phase) after stroke onset. Note that patients started rehabilitation immediately after hospitalization. Twenty-six healthy participants (mean±sd age, 63±11) were also recruited for EEG recordings. During EEG recordings, participants were asked to stay in the closed eye condition for several seconds to 2.5 minutes. To obtain phase synchronization networks, a debiased *weighted phase lag index (dwPLI)* considering to reduce spurious connectivity caused by volume conduction was computed. We derived the network community and *Flexibility Index (FI)* from the adjacency matrix of *dwPLI*. *FI* is defined as the number of times that each node changes the network community, normalized by the total number of possible changes (Bassett et al., 2011, *PNAS*). A *modularity index* was used to ensure the partition quality of the community structure.

Mean *FI* over the nodes was remarkably higher at the early sub-acute phase ($FI = 0.60$), compared with those in the late sub-acute phase ($FI = 0.57$), ($p < 0.05$). On the other hand, mean *FI* in the late sub-acute phase was comparable to the normal level observed in healthy participants. Further, looking at the *FI* of each node at early sub-acute phase, *FI* for right centroparietal channels (affected side) was positively correlated with the FMA gain but not with the FIM gain. In other words, the higher the *FI* at the early sub-acute phase was, the better the recovery from motor impairment was.

These results support the view that flexibility in network architecture is important in finding substitutable networks for specific brain functions during stroke recovery. The degree of network flexibility can be a versatile index such as diagnosis, prognosis, and brain-machine interface applications.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.02/BB5

Topic: C.09.Stroke

Support: NIH R01 HD061117
NIH R01 NS095741

Title: Structural disconnection plays a key role in brain network dysfunction after stroke

Authors: *J. C. GRIFFIS¹, J. S. SIEGEL¹, N. V. METCALF¹, M. CORBETTA², G. SHULMAN¹

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Abstract: Strokes cause focal lesions, but produce widespread functional abnormalities that can be measured by fMRI functional connectivity (FC). Abnormal FC predicts impairments, but is poorly predicted by the focal lesion. Because the structural connectome plays an important role in shaping FC in the healthy brain, we expect that its disruption shapes FC abnormalities after brain injury. To test this hypothesis, we directly compare focal damage and structural disconnection for predicting FC in 110 sub-acute stroke patients. Voxel damage was measured by mapping lesions on structural MRI, and regional damage was measured as the overlap with 359 grey matter regions from the Gordon-Laumann, AAL, and Harvard-Oxford atlases. Lesions were intersected with a population-average (N=842) diffusion MRI streamline atlas developed by Yeh et al. to obtain regional and tract disconnections. FC measures were defined based on previous reports as the average within-network interhemispheric FC, the average interhemispheric FC of the dorsal attention network (DAN), the average FC between the ipsilesional DAN and default mode network in the lesioned hemisphere, and network modularity (Newman's Q). All FC measures significantly differed between patients and demographically-matched controls (n=26). Multivariate regressions revealed that adjusted R²'s for disconnection models were on average 14% higher than for damage models, and the addition of regional or tract disconnection information significantly improved voxel and regional damage models for 3/4 and 4/4 FC measures, respectively. Disconnection models had significantly lower out-of-sample prediction error than damage models for 3/4 FC measures. Partial least squares correlations revealed a low-dimensional covariance structure between structural disconnection and FC patterns, with a single component accounting for 40% of the structure-function covariance. Model weights implicated distributed cortico-cortical, cortico-striatal, and cortico-thalamic disconnection patterns as strong predictors of abnormal FC. Further analyses revealed that undamaged but disconnected regions in different hemispheres showed significant FC

reductions compared to the same regions in controls, but revealed less consistent effects for disconnected regions in the same hemisphere. We demonstrated a key role of structural disconnection in abnormal FC after stroke. While FC abnormalities were associated with distributed disconnections, direct disconnections appeared to particularly disrupt interhemispheric FC. These results provide important insights into the structural correlates of post-stroke FC abnormalities.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.03/BB6

Topic: C.09.Stroke

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Eazysense nanotechnologies inc.
CUNY- City College of New York

Title: Intravascular blood flow displays temporal synchrony when basal ganglia neurotransmitter release is videotracked online in the normal state, while vasculature and cerebral release reflect temporal asynchrony during online videotracking of stroke: Sensing with dual laser doppler flowmetry and BRODERICK PROBE®

Authors: *R. CHOWDHURY¹, T. ALABED², S. AL AMIN², L. WENNING², P. BRODERICK²

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Abstract: Temporal synchrony, discovered in our laboratory using Live Imaging, Neuromolecular Imaging (NMI), and the BRODERICK PROBE® reveals a distinctive rhythmic regularity between cerebral blood flow and neurotransmitter release in the natural, physiologic state. However, during the pathologic state of stroke, this time sensitive rhythmicity is lost. In our study, the catecholamine, dopamine (DA) and the indoleamine, serotonin (5-HT) were imaged during baseline, experimental, acute ischemic stroke, Lovenox® (enoxaparin) therapy, and reperfusion stages on line and in vivo in an intra-animal control model. Indeed, all animals (N=16) were used as their own baseline by separately imaging the non-lesioned contralateral

brain hemisphere to obtain data for the control study group (N=16, Group A). Ipsilateral (lesioned) as well as contralateral hemispheres of dorsal striatum were imaged and Dual Laser Doppler Flowmetry (DLDF) was used concurrently to monitor cerebral blood flow. In the experimental study group (N=16, Group B), middle cerebral artery (MCA) occlusion using the nylon intraluminal suture method was performed for quantitative histopathologies via midline neck incision in order to delineate areas of infarction both before and after enoxaparin administration and subsequent reperfusion. DLDF with the sensing nanotechnology of NMI and BRODERICK PROBE® show that previous to infarction, both ipsilateral and contralateral hemispheres showed characteristic neurotransmitter synaptic release of catecholamines and indoleamines released from structures when MCA blood flow was not occluded. However, while ipsilateral MCA occlusion remained but Lovenox® therapy was administered, there was a rebound temporal synchrony between cerebral blood flow and neurotransmitter release in the brain's dorsal striatal basal ganglia. Translational brain rhythmicity between motion online with neurotransmitter release was previously reported from this lab in Medical Research Archives, 2018. Such a potent stream of evidence from reliable sources bespeaks highly of the brain's rhythmicity role in the etiology of disease.

Disclosures: **R. Chowdhury:** None. **T. Alabed:** None. **S. Al Amin:** None. **L. Wenning:** None. **P. Broderick:** None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.04/BB7

Topic: C.09.Stroke

Support: CIRM Grant DISC2-10714

Title: Use of structural and functional MRI as biomarkers for repair processes following stem cells therapy of white matter stroke

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Abstract: Stroke is the leading cause of adult disability and its incidence is expected to increase because of aging population and the increasing prevalence of metabolic syndrome. Subcortical white matter (WM) stroke constitutes up to 30% of all stroke subtypes and consists of a range of

pathophysiological events, from small infarcts to more diffuse areas of damage. There is currently no specific therapy for WM stroke, either to prevent disease progression, or to improve the brain's ability to recover from this insult.

The use of stem cells is an emerging therapy for neural repair in WM stroke. Skin fibroblasts derived induced pluripotent stem cells (iPS) can be differentiated towards Glial Enriched Progenitors (GEPs) and may be used to enhance the endogenous repair mechanisms. iPS-GEPs are ideally suited for brain repair because they differentiate into immature astrocytes, the most affected neuroglial cell population after WM stroke. Previous pre-clinical studies have shown that iPS-GEPs both replace cells lost in WM stroke and induce surviving cells to repair damaged axons.

Stem cell therapy in WM stroke is ideally suited for the development of a non-invasive biomarker of tissue repair. WM stroke regions are currently imaged as hyperintensity on T2 magnetic resonance imaging (MRI), or altered diffusivity using diffusion weighted MRI. However, there are currently no *in vivo* imaging biomarkers of the brain repair process. Therefore, in this study, we used a recently developed mouse model of WM stroke, to establish a quantitative measure of WM structure *in vivo* using structural MRI approaches involving diffusion tensor imaging metrics (FA, AD, RD and MD) throughout the repair processes that is produced by iPS-GEPs therapy. Additionally, we explored the use of resting state functional MRI as a biomarker to provide a readout of functional enhancement in cortex during the brain repair process.

The development of a biomarker of iPS-GEPs repair in WM stroke, will substantially accelerate clinical application of this iPS therapy, by enabling clinical trials to be conducted with smaller sample sizes and shorter lengths compared to current standards that use cognitive outcome measures.

Disclosures: S. Lepore: None. I.L. Llorente: None. I. Pham: None. W. Lowry: None. S.T. Carmichael: None. N.G. Harris: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.05/BB8

Topic: C.09.Stroke

Title: Associations between collateral status and histological characteristics of retrieved thrombi in patients with acute ischemic stroke

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Abstract: Background: Collateral status in acute ischemic stroke affects successful reperfusion and functional outcome. Various factors associated with collateral status were studied, however, histological findings of retrieved thrombi have never been investigated. The aim of this study is to evaluate the associations between collateral status and histologic characteristics of retrieved thrombus. **Methods:** We reviewed 124 consecutive patients with large vessel occlusion on anterior circulation over 2 years. Patients were divided into good and poor collateral groups based on collateral status from multiphase computed tomographic (CT) angiography. Retrieved thrombi from patients were analysed using semi-automated color-based segmentation method. The relative fractions of red blood cells (RBCs), congregated fibrin and platelets, and white blood cells were calculated. Thrombus patterns were dichotomized into circumferential or disseminate distribution of fibrin. **Results:** Sixty-five patients were included in this study. Seventeen patients (26.2%) showed good collateral status, and 48 patients (73.8%) were poor collateral group. In thrombus composition, fraction of RBC were higher in good collateral group ($43.8\pm 14.1\%$ vs. $31.6\pm 15.7\%$, $p=0.006$) and fibrin and platelet were lower ($51.2\pm 12.4\%$ vs. $60.6\pm 12.7\%$, $p=0.011$). WBC fraction did not differ between the two groups. Thrombus patterns were also different regarding collateral status. Circumferential pattern was more common in the good collateral group ($n=9$, 52.9% vs. $n=12$, 25.0%, $p=0.034$). **Conclusions:** This study shows that collateral scores on multiphase CT angiography are associated with thrombus composition and pattern.

Disclosures: C. Mun Hee: None. G. Park: None. J. Lee: None. S. Lee: None. J. Kim: None. J. Hong: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.06/BB9

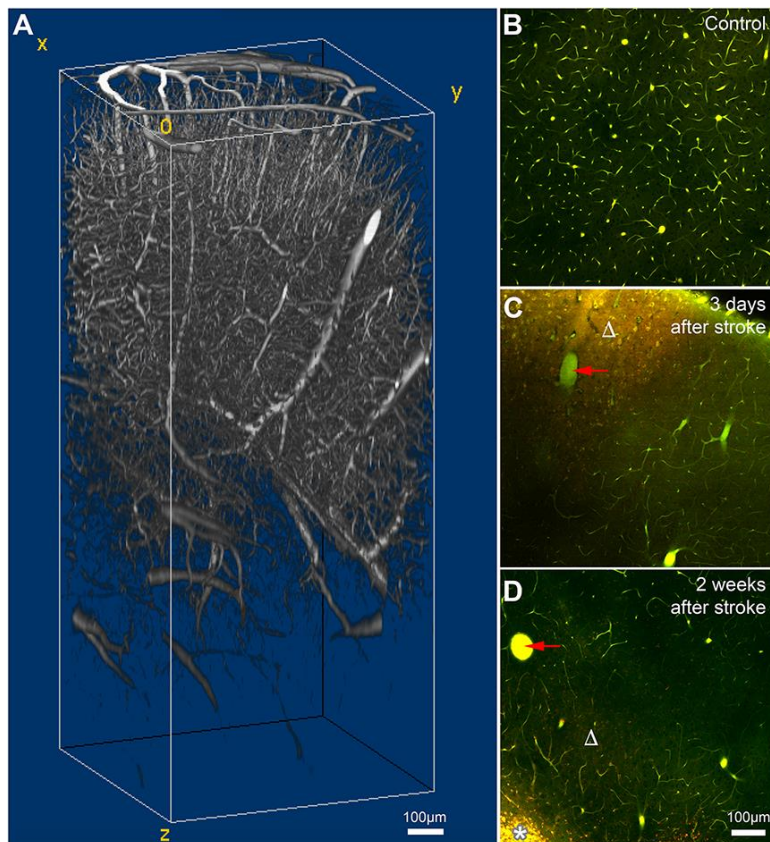
Topic: C.09.Stroke

Title: Ex-vivo angiography for deeper imaging in chronic stroke models

Authors: *K. KILIÇ^{1,2}, E. ERDENER^{1,2}, S. NING^{2,1}, S. SUNIL^{2,1}, A. CHEN^{2,1}, D. A. BOAS^{2,1}
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Abstract: Advancements in imaging technology have propelled immense progress in brain mapping endeavors. Imaging the intact brain without slicing preserves the orientation of tissue components and prevents tissue loss. Optical sectioning methods like multiphoton microscopy

allow to image deep in the tissue and detect fluorescently labeled structures. Here we present a method of fluorescein ex-vivo angiography with fructose index matching that gives us the capability to penetrate down to 2500 μm in brain tissue, therefore making it possible to image subcortical tissue with two-photon microscopy using an 800 nm laser. This method costs under \$50 per animal and takes under a week to process. The processed tissue can be preserved for future imaging sessions. Since during the processing, tissue dimension changes are minimal, the vasculature can be visualized similar to in-vivo situations without interruption of the vessel integrity. This method can be further advanced by simple astrocytic staining with SR-101 to visualize gliosis, or by multicolor imaging with transgenic and/or virus injected animals that express fluorescent probes of interest. Vessels can also be filled with other fluorophores such as Rhodamine and Alexa 680 to prevent overlap if green or yellow fluorescent proteins are expressed in the tissues. In addition, using a longer wavelength excitation laser (1300 nm as in the case of Alexa 680) can further increase the penetration depth. This method can be used to study the vascular and cellular effects of neurological disorders. Here, we present the volumetric representation of the angiography in a control animal (Fig A) and the images acquired from the chronic stroke mice compared to the healthy control (Fig B). Three days after the initiation of chronic stroke, dilated penetrating arterioles (arrow), decreased capillary density and neuronal compromise (triangle) is apparent (Fig C). After two weeks, in addition to the aforementioned findings, established infarct and surrounding gliosis (star) is observed (Fig D).



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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.07/BB10

Topic: C.09.Stroke

Support: CIHR Postdoctoral Fellowship
NIH GRANT 1R01DC008796
NIH GRANT 3R01DC008796-02S1
NIH GRANT R01DC009823-01

Title: Voxel-based lesion symptom mapping relates dorsal stream insult to severity of apraxia of speech in aphasia

Authors: *S. PAQUETTE, K. V. CHENAUSKY, A. C. NORTON, G. SCHLAUG
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Abstract: Lesion location has been used to identify regions responsible for particular deficits/impairments associated with stroke. However, when lesion location and symptomatology overlap, as in apraxia of speech (AOS) and aphasia, the extent to which each contributes to the overall communication impairment can be difficult to isolate (Hillis et al., 2004). While AOS is an acquired impairment of the ability to plan sensorimotor commands for normal speech movements (Duffy, 2013), aphasia is an acquired disorder affecting the ability to use or understand language. To examine the impact of lesion site on symptoms of these disorders, we performed voxel-based lesion-symptom mapping (VLSM) analyses in a large group of individuals to determine whether the location of brain lesions (beyond those linked to anomia) can be associated AOS symptom severity. We used the Apraxia of Speech Rating Scale (ASRS; Strand et al., 2014) to code speech samples during conversational interviews, “how-to” and picture descriptions, word/sentence repetition, and diadochokinesis assessments for 42 individuals with chronic aphasia (mean 32.4 (\pm 27.9 SD) months post-stroke). Performance on the Boston Naming Test (BNT; Kaplan et al., 1983) was used for a second VLSM analysis to contrast anomia maps with the AOS maps. For VLSM analyses, lesion masks were first drawn manually on T1-weighted images by an experienced investigator, blinded to the question of interest, and normalized using SPM8. To identify significant relationships between left-hemisphere lesioned voxel clusters and ASRS scores, MRICron’s (z-scores; Brunner-Munzel test) Non-Parametric Mapping (NPM) software was used (false discovery rate correction, $p \leq 0.01$). A critical threshold of 23% was applied (i.e., only voxels involved in at least 10 cases were used). VLSM analysis using overall ASRS scores revealed a significant white-matter cluster corresponding to the longitudinal portion of the left dorsal arcuate fasciculus (the dorsal

auditory-motor stream), distinct from the large voxel clusters associated with BNT performance. Results are consistent with the hypothesis that lesions of the dorsal stream, connecting Wernicke's and Broca's areas, interfere with the mapping of acoustics to articulation (Basilakos et al., 2015; Hickok et al., 2014; Whitewell et al., 2013) and may represent the structural correlate of AOS.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

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Program #/Poster #: 055.08/BB11

Topic: C.09.Stroke

Support: Canadian Institutes of Health Research MOP 106662
Heart and Stroke Foundation Grant-in-Aid
University of Calgary Eyes High Postdoctoral Fellowship

Title: Relationship between lesion location and performance on bimanual object hitting task

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Abstract: Introduction: Assessments and rehabilitation following a stroke typically focuses on the affected upper extremity, even though the majority of activities of daily living require bilateral upper extremity control. Through the use of a robotic object hitting task, we can assess bilateral sensorimotor control and visuospatial skills to determine how they are affected by the stroke. By combining task performance with lesion analysis, we can determine how the location of the lesion impacts different elements of performance to gain insight into the brain regions involved in bilateral visuomotor tasks.

Methods: Performance on a bilateral object hitting task was assessed at 1 week post-stroke using a KINARM exoskeleton robot in 211 participants (127 right lesions, 84 left lesions). With their upper extremities supported and viewing an augmented reality screen, participants used virtual paddles positioned at their fingertips to hit away balls that fell from the top of the screen with increasing speed and frequency. Performance was assessed across several parameters including how many targets were hit with each hand, hand speed, movement area, and spatial biases between limbs, and normalized based on age, sex, and handedness using a large control sample

(n = 598). Participants underwent acute clinical stroke imaging including FLAIR and diffusion weighted imaging sequences, and lesions were hand marked on the FLAIR images. Statistical region of interest analysis was completed separately for right and left lesions using NiiStat to determine how lesion locations impacted performance on each parameter.

Results: Overall, 76% of stroke participants had deficits in task performance compared to controls. Deficits in the total targets hit were associated with damage to the postcentral gyrus, corticospinal tract, and internal capsule for left brain lesions, and insula, precuneus, Heschl's gyrus, inferior temporal gyrus, corticospinal tract, inferior longitudinal fasciculus, inferior occipitofrontal fasciculus, internal capsule, and optic radiations for right brain lesions. The basal ganglia were implicated for both right and left brain lesions for hand speed and movement area of the contralesional hand.

Conclusions: Performance on a bimanual object hitting task is dependent on a wide network of sensorimotor and visual motor processing areas. Differences exist between right and left lesions that may be due to factors including lateralization of function, neglect, or handedness.

Understanding how lesion locations relate to performance can assist in directing therapies, as well as understanding how brain regions contribute to bimanual tasks.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.09/BB12

Topic: C.09.Stroke

Title: Modeling reaching function in chronic moderate to severe hemiparetic stroke: An interim analysis

Authors: ***G. C. BELLINGER**¹, M. D. ELLIS²

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Abstract: Many factors limit a chronic hemiparetic stroke survivor's ability to lift their affected arm against gravity and reach outwards toward an object. Possible underlying impairments affecting reaching function include weakness, loss of independent joint control (i.e., flexion synergy), flexor spasticity (i.e., hyperactive stretch reflexes), and passive range of motion limitations. The current study is using established kinematic/kinetic/electromyographic protocols to measure reaching function, single-joint strength, loss of independent joint control, and

spasticity during voluntary reaching in the same cohort of chronic stroke survivors. The values will be entered into a multiple linear regression model to determine which factors best predict reaching function. A preliminary analysis of 16 chronic stroke survivors has been conducted. The cohort has an average age of 57.82 ± 11.62 years and is collectively 11.77 ± 6.80 years post-stroke. The average upper extremity Fugl-Meyer Motor Assessment score is 27.30 ± 7.82 . Elbow extension and shoulder abduction strength were measured isometrically on both arms and the maximum voluntary torques are normalized to the unaffected side. The remaining protocols were completed in a customized robotic device including EMG of elbow flexors and extensors. The affected arm rested in a forearm-hand orthosis as the participant viewed an avatar of the upper limb and virtual targets on a screen. Flexion synergy expression was measured using a binary decision tree to determine the maximum load at which the participant could lift the arm and produce sufficient elbow extension to reach a target that was near (i.e., the takeover threshold) to or far (i.e., the emergence threshold) from the body. The participants also completed center-out forward reaches under two loading conditions to measure both flexor spasticity and reaching function. Flexor spasticity during movement was defined as the increase in biceps EMG activity from reach onset to peak angular velocity at a standardized abduction load of 50% of maximum shoulder abduction strength. Reaching function was defined as the maximum reaching distance under normal gravitational loading. The interim regression analysis of 16 participants produced a significant result ($p = 0.001$), with the emergence threshold, spasticity, and shoulder abduction strength appearing as significant regressors, supporting continued investigation. However, more participants are necessary to ensure normal distributions of all regressors and significant correlations between each regressor and the regressand (reaching function) before the model may be appropriately applied and interpreted.

Disclosures: G.C. Bellinger: None. M.D. Ellis: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.10/BB13

Topic: C.09.Stroke

Support: AHA SDG
NIH Stroke-CoBRE

Title: Diet-induced obesity exacerbates infarction and mediates hypothermia in murine experimental stroke

Authors: *X. REN¹, S. LEWIS², H. HU³, J. SIMPKINS³, E. KELLEY³

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³Physiology & Pharmacol., West Virginia University, Ctr. for Basic and Translational Stroke
Res., Morgantown, WV

Abstract: Background: Obesity/metabolic syndrome is an imminent healthcare crisis in the U.S. affecting over 30% of the population. Obesity, a state of chronic inflammation, metabolic and vascular dysfunction, is predictive of cardiovascular diseases including stroke. Previously, we have demonstrated that diet-induced obesity elevates indices of oxidative stress as well as circulating uric acid. However, it is unknown how obesity affects stroke severity and very few reports have utilized murine models of diet-induced obesity for stroke-related experimentation. As such, the goal of this study was to evaluate the role of diet-induced obesity on stroke outcomes. **Methods:** Male mice (C57/BL6J) were randomly assigned to two groups: 1) 20 weeks of high-fat feeding (60%) beginning at 6 weeks of age and 2) age-matched controls on normal laboratory chow (10%). Following 20 weeks of diet exposure, mice were subjected to transient middle cerebral artery occlusion (tMCAO, 30, 45, 60 or 90 min occlusion) following 24 h reperfusion. Cerebral blood flow was monitored by a Laser Speckle Imager. Infarct size was assessed by TTC staining and cresyl violet staining. Computational image analyses were used to quantify infarct volume while a previously described 0-5 point scale was used to assess neurologic deficits post-tMCAO. **Results:** High-fat feeding did not alter body temperature in mice prior to tMCAO. However, we observed a profound decrease in body temperature in obese mice following stroke compared to lean age-matched controls. Importantly, we observed that obese mice demonstrated larger stroke infarction by TTC staining and cresyl violet staining. Furthermore, obese mice demonstrated greater mortality and worse neurological deficits from acute ischemic injury than age-matched lean controls. **Conclusions and significance:** Our study is the first to show that obesity increases infarct size and leads to hypothermia in mice after tMCAO. These data are important in understanding the role of obesity/metabolic syndrome in stroke and providing basic knowledge to elucidate mechanisms underlying obesity/metabolic syndrome with stroke.

Disclosures: X. Ren: None. S. Lewis: None. H. Hu: None. J. Simpkins: None. E. Kelley: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.11/BB14

Topic: C.09.Stroke

Support: HHS 90IF0090-01-00

NICHD 2R01H-D039343

Title: Effects of shoulder abduction on cortical activity during attempted hand opening in moderate to severe chronic stroke

Authors: *K. B. WILKINS¹, C. CARMONA², J. P. DEWALD², J. YAO³

²Physical Therapy and Human Movement Sci., ³Physical Therapy & Human Movement Sci.,

¹Northwestern Univ., Chicago, IL

Abstract: Introduction: Hand function, particularly opening, is often significantly impaired following stroke, especially in moderate to severely impaired individuals. Unfortunately, lifting the arm, a crucial component of many activities of daily living, usually further reduces hand opening ability in this population. This is a consequence of involuntary abnormal coupling between the shoulder abductors, elbow, wrist, and finger flexors termed the “flexion synergy”. This is hypothesized to be due to increased reliance on ipsilateral corticobulbar pathways, primarily originating from secondary motor regions, following contralateral corticofugal damage. Therefore, we expect that lifting, a movement that elicits the flexion synergy, will cause increased compensatory reliance on ipsilateral secondary motor areas during attempted hand opening as contralateral resources become insufficient. Methods: We recruited 15 individuals with moderate to severe chronic hemiparetic stroke and 10 healthy age-matched controls. Individuals participated in a high-density EEG experiment in which they performed 2 tasks on an ACT3D robot: 1. Hand opening and 2. Hand opening while lifting against 50% maximum shoulder abduction (SABD) force, using the paretic (stroke) or dominant (control) hand. We then quantified the following for both tasks: 1. A Cortical Activity Ratio (CAR) for primary sensorimotor and secondary motor regions which reflects the relative strength of one region of interest compared to the entire sensorimotor cortex; 2. A laterality index (LI) which reflects the relative contribution of the contralateral and ipsilateral sensorimotor cortices. Results: The addition of lifting during attempted hand opening decreased the ratio of activity in contralateral primary sensorimotor cortex and increased such ratio in ipsilateral secondary motor areas in stroke, but not controls. This resulted in an overall increased functional reliance on the ipsilateral (contralesional) hemisphere compared to controls, specifically during the combined lifting and opening task. These findings suggest that individuals with stroke further depend on the ipsilateral hemisphere during attempted hand opening when adding in shoulder abduction, which may underlie the observed flexion synergy impairment of the arm and hand.

Disclosures: K.B. Wilkins: None. C. Carmona: None. J.P. Dewald: None. J. Yao: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.12/BB15

Topic: C.09.Stroke

Support: NIH R01HD084009-01A1

Title: Voluntary activation of the paretic elbow and wrist muscles in chronic hemiparetic stroke using twitch interpolation: Preliminary results

Authors: *L. GARMIRIAN¹, A. ACOSTA², J. P. DEWALD²

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Abstract: INTRODUCTION

Paresis, a decrease in the voluntary activation of muscles, causes weakness, and makes it difficult for stroke survivors to complete activities of daily living. The amount of paresis that occurs at specific joints in the upper extremity has not been quantified. This paper will describe the methodology and preliminary results for using twitch interpolation to quantify the ability to activate the elbow and wrist flexors and extensors in the upper limb post chronic hemiparetic stroke.

METHODS

Voluntary activation of the elbow and wrist flexors and extensors was assessed in 3 individuals post stroke. A 6 degree-of-freedom load cell was used to measure elbow torque while a single axis torque sensor was used to measure wrist torque.

A standard twitch interpolation protocol was modified to optimize measurement of the paretic upper extremity. A bipolar stimulation setup was used with one electrode over the motor point (cathode) and one electrode distal to the motor point (anode) and a single monophasic pulse was used with duration of 100 μ s.

Maximal stimulation amplitude was set at the amplitude where the measured joint torque plateaued or began to decrease. Participants were asked to relax followed by a maximum voluntary contraction (MVC). A stimulus of maximal amplitude was applied during the MVC. A second stimulus was applied after the first stimulus, with the limb back at rest. This was repeated for 6 trials.

Voluntary activation was estimated using the following formula:

Voluntary Activation = $[1 - (\text{twitch torque} / \text{resting twitch torque})] * 100\%$, where twitch torque represents the torque produced by electrical stimulation during MVC and resting twitch torque represents the torque produced by electrical stimulation with the limb at rest.

RESULTS

Preliminary results show decreased ability to activate muscle groups in the paretic, compared to the non-paretic upper limb in 3 hemiparetic individuals. Average voluntary activation of the non-paretic and paretic limb was 95% and 68% for the elbow flexors, 94% and 73% for the elbow extensors, 93% and 38% for the wrist flexors and 91% and 25% for the wrist extensors, respectively. Voluntary activation of the wrist muscles appears to be less than the elbow muscles, however, conclusions must be made cautiously due to small sample size.

DISCUSSION

This study presents preliminary data quantifying voluntary activation of the elbow and wrist muscles using twitch interpolation in 3 individuals with chronic hemiparetic stroke. The use of this method to quantify voluntary activation in the paretic upper extremity of stroke survivors will help us determine differences between proximal and distal muscles.

Disclosures: L. Garmirian: None. A. Acosta: None. J.P. Dewald: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.13/BB16

Topic: C.09.Stroke

Support: Celprogen funded R&D project

Title: The role of microglia activation and deactivation in neurological disease stages

Authors: *J. SHARMA, M. SHARMA, C. SHARMA, K. MUAINA, C. BEEZHOLD, P. GANESH, R. PUNZALAN
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Abstract: Current immune-histochemical and flow cytometric techniques have made the identification of microglia possible in routinely processed tissue sections from human brains. Glial cells, a close partner to neurons, are able to communicate with each other and with neurons through secreted proteins (Microglia Maturing Factor (MMF)) and other molecules. Secreted proteins in the extracellular environment probably play a direct role in the control and regulation of numerous biological and disease processes in the nervous system. Provision of precise diagnosis and prognosis to patients with a neurological disorder is problematic. Glial activation is a hallmark of every type of injury to the nervous system. Activated microglia often secretes inflammatory cytokines in various diseases, including Alzheimer's disease, but microglial activation is not always associated with inflammation. The equation microglial activation means "neuro-inflammation" is very interesting to some extent. The functions of microglia in the non-

diseased brain probably include a role in synaptic maintenance. A large number of tumor-associated macrophages (TAMs), which are partly derived from microglia, have been observed in glioblastoma patients. In TAMs, the expression of M2-like molecules is higher than that of M1-like molecules, but the number and differentiation state of TAMs vary in the intra-tumor area and with the type of macrophage markers used. In this model we have isolated and characterized microglia activation and deactivation with various drug candidates for treatment of various neurological disease stage.

Disclosures: **J. Sharma:** None. **M. Sharma:** None. **C. Sharma:** None. **K. Muaina:** None. **C. Beezhold:** None. **P. Ganesh:** None. **R. Punzalan:** None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.14/BB17

Topic: C.09.Stroke

Support: Department of Anesthesiology
Department of Periodontology

Title: Periodontal disease augments ischemic stroke outcomes in mice

Authors: ***A. S. AHMAD**^{1,2}, **S. S. CHUKKAPALLI**³, **P. K. KAMAT**^{1,2}, **D. HERNANDEZ**^{1,2}, **J. JIRON**⁴, **J. AGUIRRE**⁴, **L. KESAVALU**³, **S. DORE**^{1,2,5}

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Abstract: Chronic infection and persistent systemic inflammation are important risk factors for poor stroke outcomes. Chronic periodontitis (PD) are among the most common chronic immunoinflammatory infections of humans. Interestingly, in 2012, the American Heart Association reported that observational studies support an association between PD and atherosclerotic vascular disease. The association between PD and the occurrence of stroke has been explored clinically in retrospective studies. However, role of PD bacteria in hemorrhagic and ischemic stroke outcomes has not been investigated in preclinical animal models. Here we tested the hypothesis whether PD bacteria augments stroke outcomes. Ten-week-old male C57BL/6NHsd mice were randomly assigned to the infected (PD) and the sham-infected groups. Mice were infected by oral lavage with 4 periodontal bacteria (*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum*) as polybacterial infection for 12wks (inoculating 4 times per week every third week) to induce periodontitis.

Sham-infected mice was inoculated with vehicle. At the end of the 12wks infection period, mice were subjected to 60min of transient ischemia. Mice were tested for PD [bacterial infection, periodontal inflammation, alveolar bone resorption (ABR)] and functional and anatomical stroke outcomes at 48h post-stroke. All bacteria were colonized/infected in the mice gingival surface (83-100%). Polybacterial-infected mice developed mild periodontal inflammation with a trend to increased ABR. We also observed that the neurological deficit score in PD group increased by $32.40 \pm 18.56\%$ ($p < 0.01$). Similarly, the infarction volume in the infected mice ($n=7$) also increased significantly by $44.26 \pm 26.04\%$ ($p < 0.05$) as compared with controls ($n=8$). We also observed a significant difference in parenchymal bleeding in infected mice as compared with the sham-infected mice (30% vs 11%; $p < 0.001$). This is the first report demonstrating that oral bacteria induced significant neurological deficits, infarction volume, and parenchymal bleeding resulting in enhanced ischemic stroke damages.

Keywords: Cerebral ischemia, inflammation, periodontal bacteria, periodontitis, polybacterial infection.

Disclosures: A.S. Ahmad: None. S.S. Chukkapalli: None. P.K. Kamat: None. D. Hernandez: None. J. Jiron: None. J. Aguirre: None. L. Kesavalu: None. S. Dore: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.15/CC1

Topic: C.09.Stroke

Support: UT Brain seed grant

Title: Brainstem response to sensory stimuli reveals potential correlates of spasticity after stroke

Authors: *C. HAN¹, D. RESS³, S. LI⁴, J. S. SULZER²

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Abstract: Spasticity is partly characterized by a velocity-dependent resistance to passive stretch, and is common in stroke patients, but its pathophysiology remains poorly understood. Previous studies based on indirect measurements of brainstem activations have indicated two possible supraspinal descending pathways that are likely to facilitate spastic response, suggesting two hypotheses. First, reduction of inhibitory medial dorsal reticulospinal pathway is exaggerating the effects of excitatory lateral vestibulospinal activity that controls the tone of antigravity muscles and reflects laterality characteristics of spasticity. Second, the lateral imbalance itself

affects both medial dorsal reticulospinal and lateral reticulospinal pathways, thus resulting in increased stretch reflex. We aim to build a model of the dynamics causing spasticity by imaging brainstem activation through fMRI. Assuming that the imbalance of the descending pathways is the main cause of the spastic response, we implemented visual and auditory stimuli to activate lateral vestibular nuclei and/or reticular formation. We conducted two experiments on nine chronic stroke patients and seven age-matched healthy controls using two different stimuli using a 3.0T MR scanner. In the first experiment, we examined the effect of visual optokinetic motion stimuli on brainstem laterality. We exposed six stroke patients and seven age-matched controls to alternating two dimensional vection stimuli and rest. In the second experiment, we examined how an auditory stimulus triggering a startle reflex affected the functional activity of the brainstem. During the experiment, subjects were given pseudorandomized binaural bursts (>100dB) in 15 sec blocks. Analysis involved a voxel-wise non-parametric bootstrapping method. Healthy controls exhibited no distinct asymmetric response towards visual stimuli, either in number of activated voxels ($p=0.688$) or mean hemodynamic response within the activated region ($p=0.674$). However, patients showed that the number of activated voxels was lower in the ipsilesional side ($p=0.032$), with the mean of z-score in active voxels showing a trend ($p=0.129$). In response to the acoustic stimuli, healthy individuals showed no evidence of asymmetry in activated voxels ($p=0.561$) or mean z-scores ($p=0.101$). In patients, while we did not observe laterality differences due to acoustic stimuli in terms of activated voxels ($p=0.190$), there was a significant decrease in the ipsilesional mean z-score ($p=0.015$). These preliminary results offer initial evidence of possible brainstem mechanisms of spasticity. Further work is necessary to confirm these findings.

Disclosures: C. Han: None. D. Ress: None. S. Li: None. J.S. Sulzer: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.16/CC2

Topic: C.09.Stroke

Support: AHA SDG
NIH CoBRE

Title: Uncoupling of electron transport chain compromises mitochondrial oxidative phosphorylation and exacerbates stroke infarction

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Abstract: Background and Objective A cerebral infarction is a portion of necrotic tissue within the brain that occurs due to a blockage or narrowing of arteries. During vessel occlusion, oxygen and blood supply is diminished which can lead to ischemic stroke. Carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (FCCP) is a mobile ion carrier that is an uncoupling agent for the mitochondrial electron transport chain. It disrupts ATP synthesis because hydrogen ions are transported through the mitochondrial membrane before they provide energy for oxidative phosphorylation. The aim of this study is to determine the effects of uncoupling electron flow on stroke infarction. **Methods** Carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (FCCP) was used in various concentrations to measure basal respiration, ATP turnover, maximal respiration, and spare capacity in cultured cerebrovascular cells. FCCP or the vehicle was administered 30 minutes prior to transient middle cerebral artery occlusion (tMCAO) via i.p. Infarct volume was measured after a 23-hour reperfusion. Brain coronal sections were stained with TTC to measure infarct volume. **Results** FCCP significantly decreased basal respiration, ATP turnover, maximal respiration, and spare capacity compared to vehicle control. The mice that received FCCP had significantly larger infarct volume in the cortex, striatum, and total hemisphere compared to vehicle control mice. **Discussion and Conclusions** We have found that administering FCCP and uncoupling the electron transport chain leads to a larger infarct volume in the cortex, striatum, and total hemisphere. This increased volume indicates that uncoupling the electron transport chain exacerbates stroke infarction and compromises mitochondrial oxidative phosphorylation.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.17/CC3

Topic: C.09.Stroke

Support: R01HD039343

Title: Multiple stretch induced reduction in spasticity in hemiparetic stroke is short-lived

Authors: *J. R. PATTERSON¹, J. M. DROGOS², N. GURARI³, J. P. DEWALD²

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Abstract: Purpose: Spasticity is a prevalent motor impairment afflicting ~40% of individuals with chronic stroke. It is defined as a hyperactive stretch reflex and results from an increase in spinal motoneuron excitability following stroke, making muscles more resistant to stretch. Spasticity is commonly treated by repeated passive stretches of the paretic limb, which research has confirmed results in a decrease in abnormal stretch reflex torque. However, the longevity of this stretch-induced reduction is unknown yet has great implications on the efficacy of stretching as a spasticity-reducing tool.

Methods: Six participants with chronic hemiparetic stroke had their forearm casted and affixed to a robotic device that measures torque and positional data. The robotic device stretched the arm through flexion and extension about the elbow joint from 70° to 150°. Twenty stretches at 120°/s were followed by the participant activating their arm musculature by producing five ballistic extension-flexion movements, and finally by a second set of 20 stretches at 120°/s. The six participants returned to repeat the experiment with a rest period in place of the ballistic movements. The rest period was customized to be equal in duration to each participant's muscle activation period, approximately 1.5 minutes.

Results: The first set of stretches significantly reduced the abnormal biceps reflex torque. Following volitional muscle activation, biceps reflex torque returned to its initial heightened state. Following the rest period alone, biceps reflex torque returned to a less heightened state. For both protocols, the second set of stretches significantly reduced abnormal biceps reflex torque, similarly to the first set. For both sets, reflex accommodation occurred primarily within the first three stretches, then greatly decreased in the remaining stretches.

Conclusions: Stretching that evokes the stretch reflex appears to decrease motoneuron excitability, thus decreasing reflex activation post-stroke. Motoneuron excitability appears to be immediately reset upon activating the biceps and to gradually reset with rest. Findings from this study indicate that stretching only temporarily reduces elevated motoneuron excitability and thus stretch reflex hyperactivity in chronic hemiparetic stroke.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.18/CC4

Topic: C.09.Stroke

Support: DBT1517

Title: Association between c-reactive protein (crp-g1059c) gene polymorphism and its serum levels in intracerebral hemorrhage from north indian population

Authors: ***R. SAGAR**^{1,2}, A. K. YADAV¹, A. KUMAR¹, G. SHUKLA¹, D. DASH¹, A. K. SRIVASTAVA¹, S. VIVEKANANDHAN¹, A. GULATI¹, G. GUPTA², K. PRASAD¹

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Abstract: Background: CRP an inflammatory marker has been reported to be an independent predictor of Clinical outcome after ICH. Some single-nucleotide polymorphisms of CRP locus have been linked with elevated CRP levels. **Aim:** In this study, we assessed the genetic association between *CRP (G1059C)* gene polymorphism and risk of intracerebral hemorrhage. We also estimated the serum C-reactive protein (CRP) levels in intracerebral hemorrhage

Objective: The aim of this present case-control study was to investigate the association between (*CRP-G1059C*) gene polymorphisms and ICH in North Indian population. **Methods:** In this present case-control study, genotyping was performed by MALDI-TOF Mass ARRAY method for 250 patients and 250 age and sex matched controls. And serum CRP level did through ELISA. Frequency distribution of genotypes and alleles were compared between cases and controls by using conditional logistic regression. **Results:** Mean age of patients and controls were 54.98±12.8 and 55.5±12.8. 35.2% participants were female. A total of 108 (43.2%) deaths were observed. The distribution of were consistent with Hardy Weinberg Equilibrium in both groups. Conditional logistic regression analysis showed a significant association between (*CRP-G1059C*) gene polymorphism and the risk of ICH under dominant model (OR=2.09; 95% CI 1.02-4.28; p=0.04) but not in recessive model (OR 2.0; 95%CI 0.6-6.64; p= 0.26). Mean CRP was 40.6 mg/L (SD± 33.6). Cases were categorised into two groups; with bad outcome (mRS: 4-6) had significantly higher mean CRP value than patients with good outcome (mRS: 0-3) (42.9 vs 33.9; p value =0.04 ttest with unequal variance). **Conclusion:** Our results suggest that (*CRP-G1059C*) gene polymorphism may be significantly associated with the risk of ICH in North Indian population and also there is an association between serum CRP level and severity of ICH.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

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Program #/Poster #: 055.19/CC5

Topic: C.08. Ischemia

Support: Russian Science Foundation project №18-55-00229.

Title: Neurogenesis and migration of new neurons in the model of global cerebral ischemia in rats

Authors: ***M. KHODANOVICH**¹, **A. KISEL**², **M. KUDABAEVA**², **G. CHERNYSHOVA**³, **V. GLAZACHEVA**², **I. WASSERLAUF**², **M. PLOTNIKOV**³

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Abstract: Introduction: Endogenous neurogenesis is a promising target for brain ischemic recovery due to its sensitivity to brain ischemia, which enhances new neurons' production and changes the ways of neuronal migration. However, this process is poorly understood in the model of global cerebral ischemia (GCI) unlike more standardized models of stroke.

Purpose: Investigate neurogenesis and migration of new neurons in the GCI model in rats.

Methods: GCI was induced in 10 male Wistar rats by transient occlusion of three main branches of the aortic arch; 10 rats were sham-operated. Five animals from each group were euthanized at days 11 and 31 after surgery. Brain sections were immunostained for mature (NeuN) and new (DCX) neurons to evaluate neuronal damage and neurogenesis. NeuN- and DCX-positive cells were counted in the hippocampus, cortex and corpus callosum (CC).

Results: the most prominent neuronal loss was marked in the CA1 (day 11: 58.7%; day 31: 79.2%) field of the hippocampus and, to a lesser extent, in the cortex (day 11, cortical layer: 27.7%; day 31, III and V cortical layers: 41-44%). Neurogenesis in the dentate gyrus of the hippocampus was significantly increased after GCI at day 11 (71.4%) and decreased at day 31 (24.5%). A small amount of new neurons (less than 1% relative to the number of new neurons in the dentate gyrus) was observed in the damaged non-neurogenic zones of the hippocampus. A notably larger amount of new neurons (19.9% at day 11 and 87.9% at day 31) migrated from the SVZ to the CC. Part of them migrated to the damaged hippocampus (day 11: 1%; day 31: 23.6.2%) and the cortex (day 11: 8.6%; day 31: 6.2%). At day 31 migration along the CC in rats with less severe lesions caused a more than 5-fold growth whereas rats with the most severe lesions showed a low level of migration.

Conclusions: GCI causes the most significant neuronal loss in the hippocampus and, to a lesser extent, in the cortex. The SVZ may significantly contribute to hippocampal recovery in the GCI model due to migration of new neurons along the CC to the damaged hippocampus and cortex. Medium lesion causes an increase in reparative neurogenesis whereas the most severe damage depletes it.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.20/CC6

Topic: C.09.Stroke

Support: NIH Grant R01HD053793
NIH Grant R01HD073147

Title: Training out of abnormal hand synergy patterns improves dexterity in patients with chronic stroke

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Abstract: Lesions to the motor cortex and the corticospinal tract areas following a stroke cause deficits in generating isolated finger movements. Critically, in the chronic phase post-stroke, this lack of finger individuation leads to greater difficulty isolating joint movements out of a stereotyped hand posture, preventing affected people from performing basic daily functions. To date, most of conventional rehab strategies failed to improve hand dexterity in humans with chronic stroke. The aim of the current study is to investigate whether training over multiple days the affected fingers out of the flexion synergy might help restore the ability of a person with chronic stroke to actively individuate each finger and improve overall finger dexterity. We recruited 15 people who had a stroke at least 6 months prior to our testing date. Participants, first underwent baseline assessments of hand function, upper extremity impairment, and hand dexterity. This was followed by five consecutive days of training on a *piano chord-like* force device that measures isometric forces produced by each finger. Subjects completed 420 trials on each training day. Participants were instructed to simultaneously press two or three digits in a piano chord-like pattern while keeping all other fingers at rest. The trial chords selected for training were *individualized* for each patient based on his/her baseline performance. We used *reinforcement* strategies to insure high level of motivation during the *intensive* training. In order to assess performance retention and generalization, participants underwent post-training assessments one day and one week after finishing the training. Preliminary data show performance improvements in the piano chord-like task in most of our participants. This improvement was accompanied by better individuation and generalization to untrained chords. Interestingly, we have found improvements in hand functional tasks in most of the participants. The generalization to motor hand functions, like pinch precision, suggests that training improved

overall motor control (i.e. ability to individuate movements) rather than a task-specific improvement. Based on our findings, it is possible that this novel training protocol could become clinically useful to help improve finger dexterity and reduce abnormal flexion synergies in people with chronic stroke.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.21/CC7

Topic: C.09.Stroke

Support: Heart and Stroke Foundation's Canadian Partnership for Stroke Recovery

Title: A mouse model of perinatal stroke that produces targeted injury in sensorimotor cortex and contralateral impairments in forelimb function

Authors: **M. GOMEZ-SMITH**¹, I. S. TAKOFF¹, J. PITNEY², *G. SILASI¹

¹Cell. and Mol. Med., Univ. of Ottawa, Ottawa, ON, Canada; ²Cell. and Mol. Med., Julian Pitney, Ottawa, ON, Canada

Abstract: Perinatal stroke affects approximately 1 in 1500 newborns in Canada and is the leading cause of hemiplegic cerebral palsy. Most are ischemic in nature and result in damage to motor centers. Given that the neonatal brain is still undergoing extensive development, disease mechanisms and potential treatment interventions likely differ between neonatal and adult stroke. To better understand such differences, pre-clinical models are needed where both functional and structural changes can be assessed longitudinally. A photothrombotic stroke (PT) was induced in 7-day old C57BL/6 pups targeted to the right sensorimotor cortex. Infarct volume was assessed 24h after stroke using a 7T small animal MRI. Sensorimotor function was evaluated at two time points: when mice were 3 weeks old (weaned from dam) and 2 months old (adulthood). Behavioural tasks included: cylinder, DigiGait, horizontal ladder, and adhesive tape removal. A mean infarct volume of $25.4 \pm 2.3 \text{ mm}^3$ produced long-term contralateral deficits when mice were assessed in adulthood. Specifically, the stroke produced significant asymmetry in spontaneous forepaw use in the cylinder task (stroke: $35.6 \pm 16.8\%$, sham: $59.0 \pm 11.0\%$) and PT mice took significantly longer to contact the tape on the contralateral forepaw in the adhesive tape removal task (stroke: $8.4 \pm 4.5\text{s}$, sham: $2.6 \pm 0.96\text{s}$) suggesting impaired sensory processing. We did not find any deficits on skilled walking in the horizontal ladder task or gait analysis. These data establish postnatal day-7 photothrombosis as an effective model for inducing targeted strokes

within the sensorimotor system, thus mimicking the impairments present in children with perinatal stroke.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.22/CC8

Topic: C.08. Ischemia

Support: NIH KL2 grant (5KL2TR000147) to Y.A. via NCATS UL1 TR000153
UCI School of Medicine Faculty Research Grant to Y.A.

Title: Specific brain regions are activated during early arousal and recovery from post-cardiac arrest coma

Authors: M. AZADIAN, *G. TIAN, A. BAZRAFKAN, A. A. KHAN, Y. SURI, F. AGUIRRE, M. D. DESAI, I. OTAROLA, N. KHALILI, O. MIRKHANI, J. C. WANG, J. WANG, N. MAKI, O. STEWARD, Y. AKBARI
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Abstract: Cardiac arrest (CA) affects over 500,000 individuals every year in the United States alone, with an average survival rate of 10%. Upon successful cardiopulmonary resuscitation (CPR), most CA survivors emerge in a state of coma. The molecular mechanisms of coma recovery remain unknown, with limited therapeutic options for comatose patients. The ascending reticular activating system (ARAS), a classical term used to refer to a network of nuclei located throughout the brainstem, has been shown to play a critical role in maintaining behavioral arousal and consciousness. In this experiment, we assessed role of ARAS and broader ascending arousal pathways in coma arousal following CA. To evaluate this in a controlled setting, we used a rodent model of asphyxial CA with CPR to induce a comatose state. We then identified activated brain regions during early stages of neurological recovery by testing for the upregulation of c-Fos, a well characterized “immediate early gene” used as an indicator of neuronal activity. In our rodent model of CA, rats were comatose at 2 hrs post-CA and achieved near full arousal by 24 hrs post-CA, as assessed by predetermined “coma” criteria based on our behavioral testing (neurological deficit scale). We compared c-Fos expression between brain tissues collected at 2 hrs, 24 hrs, and 72 hrs post-CA, in addition to a controlled sham group (no CA but identical surgical conditions). In comparison to each group, the 2-hr post-CA brains exhibited significantly higher c-Fos expression in some regions of the ARAS, including the locus coeruleus, parabrachial nucleus, periaqueductal gray, and centromedian nucleus. This indicates

that specific regions of the ARAS are activated in very early stages of coma arousal. Moreover, our results yield several unexpected findings: (1) several regions of the ARAS, such as the tuberomammillary nucleus, have high levels of c-Fos expression in both sham and 2-hr post-CA groups, elucidating unique effects of anesthesia; (2) some brain regions, such as the thalamic reticular nucleus, are belonged to ARAS, but not activated in the 2-hr post-CA brains based on c-Fos expression; and (3) neurons in several regions outside the ARAS, such as the dentate gyrus, are activated in the 2-hr post-CA brains, but not in the sham brains. Our results indicate that specific brain regions both inside and outside the ARAS are activated during early stages of coma arousal. Determining the particular function of these specific regions may have important implications towards advancing the prospective molecular mechanisms of coma recovery as well as diagnostic and therapeutic implications for patients suffering from irrecoverable coma.

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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.23/CC9

Topic: C.08. Ischemia

Support: NIH R01-EB021018

Title: Functional ultrasound for cortical spreading depression (csd) recording in whole brain

Authors: *J. TANG¹, K. KILIÇ¹, E. ERDENER¹, D. A. BOAS²

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Abstract.Abstract1:

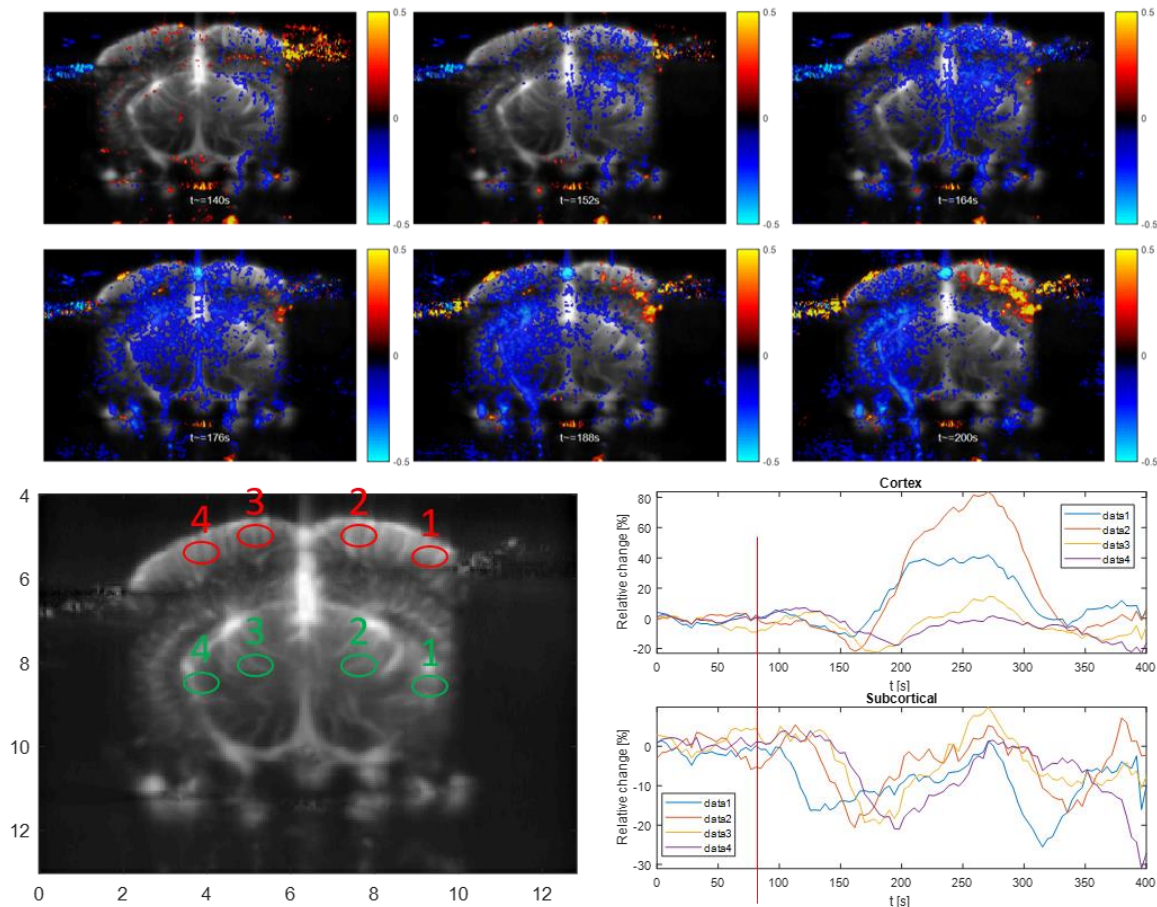
Purpose: Currently, CSD and its related blood flow changes are only studied on cortical propagation. Electrophysiological and immunohistochemistry data support that CSD may also be transmitted into subcortical structures. However, due to the lack of techniques that can provide good spatiotemporal resolution at deep penetration, there is no data on blood flow changes in the subcortical structures during CSD. Functional Ultrasound (fUS), possessing the capacities of imaging the blood flow dynamics of the whole coronal brain (mice/rats) with hundred micrometer in plane spatial and sub-second temporal resolution, lends us the ability to study subcortical hemodynamics during CSD.

Materials & Methods: In this study, an ultrafast ultrasound research system (Verasonics Inc.) was optimized for functional ultrasound (fUS) imaging. A large cranial window with a size of 10 mm 5 mm was prepared on the mice brain. CSD was induced by KCl. Animal were anesthetized with Alpha-chloralose. The fUS image was acquired for 400 s, with 80 s baseline and 320 s recording after CSD induction, and at a frame rate of 4 s/frame.

Results: Preliminary results suggest that spreading hypo-perfusion in both cortical and subcortical was detected by fUS after CSD induction as shown by Fig. 1.

Fig. 1 Hypo-perfusion spread across the whole brain after CSD induction.

Conclusion: Preliminary results show that fUS detected CSD spreading in both cortical and subcortical regions. For the next step, we will improve the fUS imaging for higher frame rate (2 s/frame) and longer acquisition time (~30 mins). In addition, we will compare fUS with electrophysiological in the subcortical regions.



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Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

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Program #/Poster #: 055.24/DP06/CC10

Topic: C.09.Stroke

Support: Georgia Tech GVU Seed Grant
Microsoft Research PhD Fellowship
NSF Graduate Research Fellowship

Title: Wearable rehab on-the-go?: Passive tactile stimulation for upper extremity rehabilitation post-stroke

Authors: *C. SEIM¹, T. ESTES², T. STARNER¹

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Abstract: We present an initial case study on wearable, vibrotactile stimulation for sensorimotor rehabilitation and spasticity reduction in 10 human stroke survivors (ages 32-67, 3 female) with disabled upper extremities.

Each year more than five million people are left disabled by stroke, making it a leading cause of long-term disability worldwide. Access to rehabilitation is often costly, time-consuming, or geographically intractable even for patients in developed nations. Furthermore, up to 50% of patients may not have enough dexterity to be eligible for therapies. We suggest that wearable vibrotactile stimulation may enable mobile therapy without required exercises.

Previous work has examined targeted muscle vibration to improve motor activation, whole-body vibration for spasticity reduction, and surface electrostimulation to improve sensation after stroke or SCI. Furthermore, many robotic systems integrate vibrotactile stimulation into their interactive therapies; in contrast, we examine mobile, wearable stimulation alone without required exercises. In a preceding experiment, we found sensation improvements in partial Spinal Cord Injury patients with disabled hands after they wore a vibrotactile glove five times per week for two months. Now we examine this 'passive tactile stimulation' technique for stroke rehab.

Stroke survivors (1-12 years post-stroke) with disabled hand movement are given a rechargeable vibrotactile glove to take home and instructed to wear it vibrating for 3hr. daily during their normal routine. Active range of motion, cutaneous sensation, spasticity and unilateral spatial neglect are measured throughout the eight weeks of the study. Ten experimental patients have been studied and results suggest significant improvement in active range of motion, cutaneous sensation and spasticity. Control patients do not reflect the same changes. An initial cohort of six participants all received experimental glove treatment. Followed by a cohort of four who were

randomly assigned to experimental or sham treatment, but not told of their assigned condition. The two controls were given the option to receive the experimental condition after finishing the 8 weeks of blind sham condition. Results of this exploratory research suggest that passive tactile stimulation applied to the disabled upper extremity may aide recovery; possibly enabling a low-cost, wireless, wearable computing glove to provide therapy on-the-go or at home.

Disclosures: T. Estes: None. T. Starner: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.25/CC11

Topic: C.09.Stroke

Support: Departmental funds

Title: Endovascular thrombectomy of acute ischemic stroke leads to beneficial outcome in a tertiary community center

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Abstract: The benefits and safety of endovascular treatment for acute ischemic stroke performed in community centers is unknown. Therefore, the purpose of this study is to determine the neurological outcome and overall mortality and complication rates in patients undergoing endovascular thrombectomy for acute ischemic stroke in a tertiary community centre. The results will be compared to published reports of prospective randomized multicenter trials. The study is a retrospective analysis of a cohort of acute ischemic stroke patients admitted during 2016 to the Trillium Health Partners (THP). Patients included in the analysis had large cerebral vessel occlusion of the anterior circulation based on CT-angiography findings. Exclusion criteria were endovascular thrombectomy with failure to introduce the stent, history of previous stroke, and adverse events related to tissue plasminogen activator (tPA). A total of 65 patients were reviewed. Ten patients were excluded due deficient charts. In five patients, there was failure to introduce the stent. Hence, 50 patients were analyzed. The mean(S.D.) age was 71.7(14.1) years. The admission systolic blood pressure and blood sugar were 153(29) mmHg and 8(2.7) mmol/L. Two thirds of patients were admitted directly to THP. Seventy percent of patients had IV tPA treatments prior to the procedure and the stroke-tPA time was 111(45) minutes. The CT-reperfusion and stroke-reperfusion times were 157(48) and 261(98) minutes respectively. The

total length of hospital stay after procedure was 10(12) days. The table below shows neurologic functional outcome at more than 90 days post-stroke compared to the ESCAPE and SWIFT PRIME multicentre trials. Overall mortality at THP and in the SWIFT PRIME trial was 13.4 and 9% respectively. Additionally, serious adverse event rate in THP was 32%, while in the ESCAPE trial patients was 36%. We conclude that endovascular treatment for acute ischemic stroke can be done efficiently and safely in a prepared tertiary community center.

Comparison between THP, ESCAPE trial, and SWIFT PRIME trial patients			
>90 days Modified Rankin Score	THP (n=50)	ESCAPE trial (n=119)	SWIFT PRIME trial (n=98)
0	9/50 (18%)	15/119 (13%)	17/98 (17%)
1	11/50 (22%)	25/119 (21%)	25/98 (26%)
2	11/50 (22%)	21/119 (18%)	17/98 (17%)
3	8/50 (16%)	21/119 (18%)	12/98 (12%)
4	3/50 (5%)*	21/119 (18%)	15/98 (15%)
5-6	8/50 (16%)	17/119 (14%)	12/98 (12%)
*Indicates statistical significance from ESCAPE trial (p<0.05)			

Disclosures: I. Cheema: None. R. Dominic: None. S. Jhas: None. M. Shahideh: None. L. Looi-Lyons: None. H.E. El-Beheiry: None.

Poster

055. Stroke Imaging and Diagnostic Studies: Vascular and Movement Emphasis During Recovery

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 055.26/CC12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Stroke symptomology, rare infectious etiology

Authors: *F. P. MELENDEZ¹, A. DAVIS¹, D. CASADESUS², K. SHILLINGFORD², A. MENDELSON³, E. MENDEZ¹

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Abstract: Introduction: Hemiparesis and facial droop are common symptoms of cerebrovascular disease. Time is of the essence in acute evaluation of stroke. Early diagnosis is

paramount in establishing treatment, morbidity and mortality. Most cases are guided by history, physical examination and a non-contrast CT scan. Our case presents to the hospital with hemiparesis, ataxia, slurred speech and facial droop. Further studies revealed Progressive Multifocal Encephalopathy (PML).

Case description: A 35 year old African American female with a history of AIDS and cocaine abuse, presented with right-sided weakness for one month, associated with dysphagia. Upon physical examination she had facial maculopapular rash, oral Thrush, right side hemiplegia, ataxia, facial droop, and a positive Romberg sign. Initial non-contrast head CT showed no abnormalities. Follow up contrast CT exhibited a left frontal lobe lesion involving white matter with mild edema. Serology indicated Toxoplasma IgG. Patient's CD4 count was 18. Lumbar puncture was positive for EBV DNA and JC virus DNA. Brain biopsy then performed demonstrated multiple areas of demyelination with reactive gliosis, bizarre astrocytes, lymphoplasmocytic inflammation and enlarged oligodendrocyte nuclei to confirm PML diagnosis. Patient was initiated on HAART, Fluconazole and TMP-SMX. She was discharged 16 days later with resolution of the facial droop and improvement of hemiparesis and ataxia. Three months later the patient was readmitted with new onset metabolic encephalopathy and seizure. No opportunistic infection was detected but EEG displayed Status Epilepticus. She was treated with antiepileptic medication and Acyclovir. Patient returned to baseline, and remains alive today.

Discussion: Sudden loss of focal brain function is the kernel feature of the onset of ischemic stroke. In patients with AIDS and negative initial CT scan of the brain, infectious causes should be considered. PML, with its high mortality rate makes controlling AIDS with effective HAART therapy all the more important. Strong clinical suspicion and knowledge of infectious etiology is critical.

Disclosures: **F.P. Melendez:** None. **A. Davis:** None. **D. Casadesus:** None. **K. Shillingford:** None. **A. Mendelson:** None. **E. Mendez:** None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.01/CC13

Topic: C.10. Brain Injury and Trauma

Support: Australian Research Council Future Fellowship (FT120100030).

Australian Research Council Linkage Project (LP120200081)

Australian National Health and Medical Research Council Career Development Fellowship (APP1120582)

Title: Trehalose elevates brain zinc levels following a controlled cortical impact brain injury in aged mice

Authors: *S. D. PORTBURY¹, D. J. HARE¹, D. P. BISHOP², P. A. DOBLE², D. I. FINKELSTEIN¹, P. A. ADLARD¹

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Abstract: Zinc (Zn) deficiency is a clinical consequence of brain injury that can result in neuropathological outcomes that are exacerbated with age. Trehalose is a stable disaccharide that has previously demonstrated therapeutic efficacy in a mouse model of TBI, and other neurodegenerative mouse models *via* a diverse array of mechanisms including autophagy, growth factor promotion, and oxidative stress reduction. Given these observations, we examined trehalose as a potential modulator of Zn homeostasis in aged (24-month-old) mice receiving a controlled cortical impact (CCI) TBI. Spatial and temporal concentrations of zinc were assessed in trehalose treated, non-treated and uninjured mouse brains post-TBI utilizing laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) imaging techniques. Trehalose-treated animals revealed an overall significant elevation of Zn concentration in both the ipsilateral and contralateral hemisphere when compared to vehicle-treated animals, restoring brain zinc concentrations to equal or greater levels than uninjured sham animals. These observations provide important preliminary data for larger studies using this simple carbohydrate as a modulator of this essential micronutrient after TBI. Our results may have further implications for the treatment of a variety of neurodegenerative diseases and other disorders of the nervous system.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.02/CC14

Topic: C.10. Brain Injury and Trauma

Support: DoD Congressionally Directed Medical Research Programs (CDMRP) AZ140109 and Peer Reviewed Alzheimer's Research Program (PRARP) Convergence Science Research Award
Department of Pathology & Anatomical Sciences at the University of Missouri School of Medicine

Title: Characterization of mitochondrial damage due to low-intensity primary blast injury

Authors: *H. SONG¹, L. M. KONAN¹, J. CUI¹, C. E. JOHNSON⁶, M. LANGENDERFER⁶, D. G. GRANT², B. YANG³, X. WANG⁷, T. WHITE², M. GREENLIEF³, U. DEMIRCI⁸, G. Y. SUN⁴, G. K. HUBLER⁵, R. SWERDLOW⁷, I. CERNAK⁹, R. G. DEPALMA¹⁰, Z. GU¹
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Abstract: Combat traumatic brain injury (TBI) is often called a ‘*signature wound*’ of modern military conflicts. The Department of Defense reports 375,230 TBIs acquired during 2000-2017 (Q1-Q4) and mostly inflicted by explosive weaponry. Over 82% of all TBIs were classified as mild TBI/concussion. Our previous observations reveal ultrastructural changes in the brain and behavioral impairments that developed parallel as a result of a low-intensity open-field blast exposure in a mouse model. These injuries occurred in the absence of acceleration with no gross or microscopic pathology in the brain or other organs. Our current study focuses on mitochondrial (MT) damage and associated biochemical changes in animals exposed to differing blast intensities. Methods: This *Missouri blast* model used C57BL/6J mice in prone position exposed to open-field blast by detonation of 350 grams of high-energy C4 explosive. The blast intensity depended on the animals’ distances at 2.15~7 meters (m) from the explosive charge. The frequency and types of MT damage were assessed by transmission electron microscopy (TEM). MT associated biomarkers, including 4-HNE and SOD2 for oxidative stress, Drp1 and OPA1 on fission-fusion dynamics together with key electron transport chain enzymatic activities were measured to delineate MT functions. Results: The *Missouri blast* set-up generated a primary blast wave with peak overpressures from 80.7 to 20.0 kPa and maximum impulses 71.0 to 29.7 kPa *ms, depending on the animal distance (2.15~7 m) from the source of explosion. Under TEM, swollen and degenerated MT within the neuropil were detected. Further analysis of mitochondrial markers showed significantly increased generation of reactive oxygen species and acutely impaired mitochondrial dynamics in mice closest (2.15-m) to the source of explosion as compared to the 3-m group. Moreover, we observed compromised MT respiration activity (complex I) after blast exposures. These preliminary results suggested that compromised MT-associated functions depend on the static overpressure and dynamic impulse. Conclusions: Our observations demonstrated that low-intensity primary blast injury causes nanoscale MT damages associated with early increases in oxidative stress and compromised respiratory activity. These findings provide insights into the pathogenesis of primary blast injury. Further investigations are underway to delineate causes and downstream effects of MT damage.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.03/CC15

Topic: C.10. Brain Injury and Trauma

Support: Fondation Leducq
CIHR
MSFHR

Title: Brain pericytes are mesenchymal progenitors that support cerebrovascular regeneration after stroke

Authors: ***L.-P. BERNIER**¹, J. K. HEFENDEHL¹, C.-A. LEWIS², W. R. SCOTT², F. M. ROSSI², M. T. UNDERHILL², B. A. MACVICAR¹

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Abstract: Brain pericytes of the neurovascular unit are critical for the developmental maturation of cerebral blood vessels and for the integrity of the blood-brain barrier (BBB). Pericytes are perivascular mural cells that share similarities with mesenchymal progenitors (MP), a cellular pool critical in supporting tissue regeneration. Therefore we examined what role brain pericytes play in repairing and restoring the cerebral microvasculature following stroke using a new transgenic MP reporter mouse. We show that after stroke, pericytes enter the cell cycle to support cerebrovascular regeneration in a manner similar to their role during development. Following stroke, pericytes proliferate and migrate into the infarct region where they accumulate inside a border of reactive astrocytes. The pericyte-astrocyte interface forms an angiogenic zone that progressively migrates into the ischemic core, thereby supporting a wave of tissue revascularization. Within a few weeks normal vessels with an intact BBB are found perfusing the previously ischemic cortical area. Using single-cell and population RNA sequencing, we identify transcriptional signatures of naïve pericyte subpopulations as well as a functional and transcriptional profile of activated pericytes following trauma. Brain pericytes in the adult brain represent a major progenitor population that can modify their phenotype to contribute to the regeneration of cerebral blood vessels following injury in a process that recapitulates their role in developmental vasculogenesis.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.04/CC16

Topic: C.10. Brain Injury and Trauma

Support: Canadian Institutes of Health Research MOP#142231
MS Society of Canada

Title: Cuprizone-induced iron overload and oligodendrocyte loss in the corpus callosum

Authors: *P. JHELMUM, E. SANTOS-NOGUEIRA, A. HAUMONT, I. LENOËL, S. DAVID
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Abstract: The copper chelator, cuprizone (CZ), induces oligodendrocyte (OL) death and demyelination in the CNS, which is seen particularly well in the corpus callosum. Copper chelation will reduce availability of copper for copper-containing enzymes, which are involved in cellular iron efflux. Therefore, CZ treatment can be expected to alter iron homeostasis in OL and other cell types and lead to iron accumulation and cell death. As iron is needed for remyelination, increased iron in macrophages may be beneficial during the late remyelination phase. In this study, we assessed the loss of mature OL from 2 days to 5 weeks after start of CZ treatment, and correlated this with changes in expression of ferritin, a surrogate marker for cellular iron. Mature CC1+ OL showed a sharp loss at 2 days, decreasing further at 1 week, followed by a gradual increase up to 3 weeks. This was followed by a second phase of cell loss at 4 weeks and full recovery at 5 weeks. This suggests two cycles of cell death. The early loss of OL is correlated with a reduction in mRNA for the OL-specific iron efflux protein, hephaestin, at 1 week. In addition, there is an increase in HO-1 and reduction in SOD-1 at 1-week which may underlie OL cell death. Lipid peroxidation assessed by 4HNE showed increase at 1 week (phase of OL loss) followed by greater increase between 3-4 weeks (demyelination phase). Densitometry for ferritin immunolabeling showed a ~2 - 3-fold increase at 2 and 3 weeks, a sharp reduction at 4 weeks followed by a second phase increase by 3-fold at 5 weeks. The first increase in ferritin occurs in OL, and the second increase occurs in macrophages. This increase of iron in macrophages at 5 weeks is correlated with increased mRNA expression of ferroportin and ceruloplasmin, which is required for iron efflux. Thus, making iron available for remyelination. Our results also suggest a remobilization of copper into the CNS at late stages (5 weeks). In addition, the very early loss of OL (at 2-4 days) is correlated with changes in the expression of ferroptosis markers (COX-2, TfR1, ferritin-H). Ferroptosis inhibitors are currently being tested. These results suggest that loss of copper may contribute to iron-mediated OL death at the early time points (2 days -2 weeks), and the later increase in macrophages (5 weeks) which may have a role in remyelination.

Disclosures: P. Jhelum: None. E. Santos-Nogueira: None. A. Haumont: None. I. Lenoël: None. S. David: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.05/DD1

Topic: C.10. Brain Injury and Trauma

Support: NIH grants RO1NS089901

Title: Oncogenes src and rock play critical roles in traumatic brain injury

Authors: *D. LIU¹, B. P. ANDER¹, F. R. SHARP¹, B. G. LYETH²

¹Neurol., ²Neurolog. Surgery, UC Davis, Davis, CA

Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability, but there is no currently FDA approved drugs for treating TBI. To explore new therapeutic approaches for TBI, we proposed a new concept of “aberrant cell cycle disease” wherein oncogenes promote cell division in cancer but the same genes drive mature neuron entry into the cell cycle which results in apoptotic neuronal death. Moreover, oncogenes promote cancer cells crossing from blood into tissue to cause metastasis. Since many oncogene inhibitors have been well tolerated when taken chronically in cancer clinical trials and approved by FDA, short-term use of these drugs would also be safe for treating TBI.

Therefore, we hypothesized that oncogene inhibitors (e.g., Src inhibitor PP2, ROCK inhibitor Y27632) that treat cancers can be repurposed to treat TBI. Using lateral fluid percussion injury (LFP)-induced TBI model, we demonstrated that Src inhibitor PP2 or ROCK inhibitor Y27632 promotes cognitive function assessed at 11 through 15 days after TBI in Morris water maze, and improves survival of hippocampal neurons (NeuN⁺ cells) at 16 days after TBI. In addition, we found that inhibiting oncogenes maintains endothelium integrity, reduces BBB disruption and decreases water content in ipsilateral cortex after TBI in rats. Using *in vivo* nanoparticle-based siRNA transfection system, we further demonstrated that combined inhibition of two Src subtypes (Fyn, c-Src) improve TBI outcomes.

In conclusion, inhibiting oncogenes (e.g., Src, Rock) improves multiple outcome measurements after TBI in rats. This study provides a proof of principle: repurposing cancer drugs (oncogene inhibitors, tumor suppressor mimics) to treat TBI.

Disclosures: D. Liu: None. B.P. Ander: None. F.R. Sharp: None. B.G. Lyeth: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.06/DD2

Topic: C.10. Brain Injury and Trauma

Support: NS085046
NS096012
NS045540
NS082174

Title: Selective vulnerability of hippocampal interneurons to graded traumatic brain injury

Authors: ***J. C. FRANKOWSKI**, Y. J. KIM, R. F. HUNT
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Abstract: Traumatic brain injury is a major risk factor for the development of long-term cognitive deficits and post-traumatic epilepsy. Controlled cortical impact (CCI) is a widely-used model of contusive brain injury that produces hippocampal cell loss, reductions in synaptic inhibition, and spontaneous seizures in mice. However, it is currently unknown how distinct populations of interneurons are affected by CCI injury. Here we quantified the density of inhibitory interneurons in dorsal hippocampus of GAD67-GFP reporter mice 30 days after moderate (0.5mm impact depth) or severe (1.0mm impact depth) CCI injury. Brain injured mice displayed subfield and cell-type specific decreases in interneurons after impact depths of 0.5mm and 1.0mm, and increasing the depth of impact led to greater cell loss. In all regions of hippocampus, we found a preferential reduction of interneuron cohorts known to provide feedback inhibition to excitatory principal neurons, while interneurons positioned to provide feed-forward inhibition appeared well preserved. Our results suggest a dramatic shift of interneuron diversity following contusion injury that may contribute to the pathophysiology of traumatic brain injury.

Disclosures: **J.C. Frankowski:** None. **Y.J. Kim:** None. **R.F. Hunt:** None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.07/DD3

Topic: C.10. Brain Injury and Trauma

Support: NIH grant NS073779

AHA grant 18POST34070061 (anticipated start date: 7/1/2018).

Title: Exposure to recurrent hypoglycemia modulates endoplasmic reticulum stress in hippocampus of insulin-treated diabetic rats

Authors: *A. K. REHNI¹, K. R. DAVE²

¹Neurol., Univ. of Miami Sch. of Med., Miami, FL; ²Neurol., Univ. of Miami Miller Sch. of Med., Miami, FL

Abstract: Diabetes is a chronic metabolic disease and stroke or cardiac arrest in diabetics' causes a wide spread ischemic brain injury. Drug therapy for diabetes induces episodes of hypoglycemia. Repeated events of such hypoglycemia leads to hypoglycemia associated autonomic failure and results in the exposure of diabetes patients to recurrent hypoglycemia (RH). We have previously shown that preceding exposure of RH enhances ischemic brain damage in insulin-treated diabetic (ITD) rats. Nevertheless, the mechanistic basis of this increased injury is not well understood. A single episode of moderate hypoglycemia activates unfolded protein response in liver. Glucose starvation activates endoplasmic reticulum (ER) stress in cultured hippocampal neurons. We have shown that ischemia causes a significant increase in the levels of protein kinase RNA-like endoplasmic reticulum kinase (PERK) phosphorylation and C/EBP homologous protein (CHOP) levels in hippocampus of ITD rats previously exposed to RH. However, the effect of RH on the levels of these markers of ER stress in ITD rats is unknown. Therefore, we tested the hypothesis that prior RH exposure modulates ER stress in the hippocampus of ITD rats. ER stress in ITD rats was evaluated by determining the levels of total and phospho-PERK, and CHOP (using western blot analysis) in Naïve (n=6), ITD (n=6), and ITD + RH (representing RH-exposed diabetes patients) (n=6) groups. Male Wistar rats were made diabetic using a dose of streptozotocin and after 2-3 weeks, insulin pellet(s) were implanted to treat diabetic hyperglycemia. After 2-3 weeks of treatment, an additional dose of insulin was given to elicit hypoglycemia for 3 hours every day for 5 days. Hippocampi were harvested overnight after last episode of hypoglycemia. We found that the phosphorylated PERK (pPERK) to total PERK ratio in the group of RH-exposed ITD rats was higher by 74% (P<0.05) and 35% (P<0.05) as compared with naïve and ITD groups, respectively. Total PERK levels in the group of RH-exposed ITD rats was lower by 54% (P<0.05) and 45% (P<0.05) as compared with naïve and ITD groups, respectively. RH did not exert any significant effect on protein levels of CHOP in the hippocampus as compared with naïve and ITD groups. Therefore, we conclude that prior exposure of RH decreases the levels of PERK in ITD rats and may play a role in increased cerebral ischemic damage in RH-exposed ITD rats. Understanding the role of ER stress in RH-induced aggravation of ischemic brain damage may help in developing new therapeutic options for diabetic patients experiencing stroke or cardiac arrest.

Disclosures: A.K. Rehni: None. K.R. Dave: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.08/DD4

Topic: C.10. Brain Injury and Trauma

Support: Center for Neuroscience and Regenerative Medicine Grant CNRM703386
Congressionally Directed Medical Research Program Grant SC160213

Title: Experimental traumatic brain injury identifies distinct early and late phase axonal conduction deficits of white matter pathophysiology, and reveals intervening recovery

Authors: *C. M. MARION^{1,2}, K. L. RADOMSKI^{2,3}, N. P. CRAMER^{2,3}, Z. GALDZICKI^{1,2,3}, R. C. ARMSTRONG^{1,2,3}

¹Program in Neurosci., F. Edward Hebert Sch. of Medicine, Uniformed Ser, Bethesda, MD; ²Ctr. for Neurosci. and Regenerative Med., ³Dept. of Anatomy, Physiol. and Genet., F. Edward Hebert Sch. of Medicine, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Traumatic brain injury (TBI) patients often exhibit slowed information processing speed that can underlie diverse symptoms. Processing speed depends on neural circuit function at synapses, in the soma, and along axons. Long axons in white matter (WM) tracts are particularly vulnerable to TBI. We hypothesized that disrupted axon-myelin interactions that slow or block action potential conduction in WM tracts may contribute to slowed processing speed after TBI. Concussive TBI in 8-10 wk old male/female mice was used to produce traumatic axonal injury in the corpus callosum (CC), similar to WM pathology in human TBI. Compound action potential velocity was slowed along myelinated axons at 3d post-TBI with partial recovery by 2 wks, suggesting early demyelination followed by remyelination. Ultrastructurally, dispersed demyelinated axons and disorganized myelin attachment to axons at paranodes were apparent within CC regions exhibiting traumatic axonal injury. Action potential conduction is exquisitely sensitive to paranode abnormalities. Molecular identification of paranodes and nodes of Ranvier detected asymmetrical paranode pairs and abnormal heminodes after TBI. Fluorescent labeling of oligodendrocyte progenitors in *NG2CreERTM;mTmG* mice showed increased synthesis of new membranes extended along axons to paranodes, indicating remyelination after TBI. At later times post-TBI, an overall loss of conducting axons was observed at 6 wks followed by CC atrophy at 8 wks. These studies identify a progression of both myelinated axon conduction deficits and axon-myelin pathology in the corpus callosum, implicating white matter injury in impaired information processing at early and late phases post-TBI. Furthermore, the intervening recovery reveals a potential therapeutic window.

All data collection and analysis was performed by investigators blinded to the condition. Mice for electrophysiology were analyzed in yoked sham/TBI pairs, $n \geq 4$ mice per condition. Multiple

sections from at least 2 electron microscopy grids were assessed per mouse, $n \geq 3$ mice per condition. Immunofluorescence of transgenic mice directly compared littermates, when possible, using at least 2 confocal images/section or 4 wide-field images from multiple sections per mouse, $n \geq 3$ mice per condition.

Disclosures: C.M. Marion: None. K.L. Radomski: None. N.P. Cramer: None. Z. Galdzicki: None. R.C. Armstrong: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.09/DD5

Topic: C.10. Brain Injury and Trauma

Support: NIH R01 NS091218

Title: Crosstalk between autophagy and neuroinflammation following traumatic brain injury

Authors: *N. U. HEGDEKAR¹, C. SARKAR³, P. RAVISHANKAR², D. PHILKANA, 21201², M. M. LIPINSKI⁴

¹Dept. of Anesthesiol., ²Univ. of Maryland Baltimore, Baltimore, MD; ³Shock, Trauma and Anesthesiol. Res. (STAR) Center, Dept. of Anesthesiol., ⁴Anesthesiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The autophagy-lysosomal pathway serves an important role in cellular homeostasis and protection against neurodegeneration. Recently autophagy has been also implicated in regulation of immune and inflammatory responses. Specifically, high levels of autophagy flux - the progress of substrates through autophagic compartments leading to their delivery and degradation in the lysosomes - are generally associated with anti-inflammatory, and inhibition of flux with pro-inflammatory phenotypes. To determine if autophagy may be involved in modulation of brain inflammation after TBI, we assessed the levels of autophagy in resident microglia and infiltrating macrophages following moderate controlled cortical impact (CCI) in *C57Bl/6* mice. Consistent with a potential function in neuroinflammation, we observed accumulation of autophagosomes and inhibition of autophagy flux specifically in the activated microglia/macrophages. Our studies using transgenic *Cx3Cr1-GFP* microglial and *Ccr2-RFP* monocyte reporter mice demonstrated that infiltrating macrophages are affected by the block of autophagy flux to a much higher degree than activated resident microglia. Autophagy impairment in the activated cells of the microglia/macrophage lineage peaked at day 3 post-CCI and persisted at least through day 7. At day 3 after CCI, the cells with inhibited autophagy reveal a mixed (transitional) inflammatory phenotype, characterized by expression of both pro- and anti-inflammatory polarization markers. Since the transitional immune cells are believed to

preferentially switch to pro-inflammatory fates, we hypothesize that inhibition of autophagy within these cells could promote their pro-inflammatory polarization after TBI. This is supported by our *in vitro* experiments demonstrating that inhibition of autophagy can potentiate pro-inflammatory activation induced by LPS treatment of BV2 microglial cells and *in vivo* data showing altered expression of inflammatory markers in autophagy hypomorph *Becn1*^{+/-} mice after injury. These findings provide insights into the molecular crosstalk between autophagy and neuroinflammation following brain injury.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.10/DD6

Topic: C.10. Brain Injury and Trauma

Support: NIH NS094908

Title: A novel bioluminescent reporter confirms an increase in extracellular ATP in the brain following a traumatic brain injury: Implications for downstream pathologies

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Abstract: Background: Epidemiological studies suggest increased risk of developing Parkinson's disease (PD) in individuals who have experienced a traumatic brain injury (TBI). Neuropathologically, PD is characterized by the loss of dopaminergic neurons in the substantia nigra, and intracytoplasmic accumulation of aggregated alpha-synuclein (α syn) in neurons. Interestingly, patients experiencing severe TBI have increased α syn CSF levels, and animal models of TBI have reduced striatal dopamine levels. This suggests that pathophysiological mechanisms underlying PD are linked to the effects of a TBI; however the associated mechanisms remain to be determined. *In vitro* data from our lab suggests that extracellular ATP (eATP) released from injured or dying cells can facilitate α syn aggregation via P2X1 receptors. To further investigate these findings, we developed a novel *in vivo* model to monitor changes in eATP following a TBI. Here we used a bioluminescent eATP reporter called pmeLUC to monitor the change in photon flux before and after a controlled cortical impact (CCI) in mice. PmeLUC is a modified version of firefly luciferase that contains both a plasma membrane localization signal and a GPI anchor. **Methods:** PmeLUC was subcloned into an AAV vector

and high titer AAV2/9 was injected into the lateral ventricles of neonatal (P0) mice to generate whole brain expression of pmeLUC. Animals were aged to two months before being subjected to a CCI of 3m/s at a depth of 1mm. As control, a sham group underwent craniotomy only. Immediately after CCI or sham surgery, animals were imaged using a Spectrum *in vivo* imaging system (IVIS) to record photon flux. The change in the eATP signal was then calculated by dividing the photon flux by the maximum photon flux established during a pre-CCI/sham baseline imaging session. **Results:** Animals subjected to a moderate TBI (n=7) had a 22% increase in eATP signal compared to sham animals (n=5) (p=0.0006; two-way ANOVA analysis). To validate the change in photon flux was due to eATP, animals were injected IV with recombinant human apyrase immediately prior to CCI. Apyrase treated animals (n=6) had an insignificant increase in eATP signal of 7% compared to the sham group. **In summary,** our data support the use of pmeLUC as a live-animal reporter of eATP in brain. To our knowledge this is the first time eATP has been monitored in the brain in real time. Our data support a significant release of eATP following a moderate TBI. Current studies are focused on the association of downstream α syn pathology and increased eATP following a TBI.

Disclosures: P.J. McLean: None. A.H. Faroqi: None. M. Delenclos: None. E.C. Kee: None. J.H. Lee: None. J.D. Burgess: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.11/DD7

Topic: C.10. Brain Injury and Trauma

Title: *In vitro* quantitative analysis of neuronal electrical changes following mechanical loading

Authors: *A. DILEONARDI¹, E. A. MATHEIS², K. RAFAELS¹

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Abstract: Traumatic brain injury (TBI) occurs when an external mechanical force causes brain dysfunction. Fundamentally, the brain is damaged through distortion or straining beyond a certain tolerance. To design the best protection to prevent TBI, it is important to understand the tolerances of brain tissue. Previous work has shown that different regions of the brain exhibit different material properties [Elkin 2011, Finan 2012], potentially leading to varying tolerances. One theory to explain this difference is regional differences in the neuron/glia ratio [Meaney 2014]. Considering the complex structural and functional interactions with the brain, our approach to understanding the influence of mechanical loading on the brain is to systematically injure a mixed culture of primary pyramidal neurons and astrocytes *in vitro* with known loading conditions and quantify measures to separately evaluate structural and functional alterations.

These cells were grown on deformable membranes and subjected to a biaxial stretch of increasing strain. To obtain the unique cellular responses of each cell type after the mechanical insult, individual cells were tracked using live-cell imaging prior to and post-stretch to determine immediate structural alterations. The neurons demonstrated neurite beading and breakage as well as a reduction in total neurite length after stretching. Stretching of the glia caused morphological changes such as vacuolization and disruption of glial filaments. The amount of structural alterations is positively correlated to the membrane deformation. Functional damage was evaluated using additional cultures plated on microelectrode arrays embedded within silicone membranes. The MicroElectrode Array Stretching Stimulating und Recording Equipment (MEASSuRE) device was utilized to strain neuronal cultures, as well as quantify changes in electrophysiological activity during, and immediately following the mechanical loading in one continuous data stream. The maximum stimulus response of the cultures was reduced after stretching. In summary we have developed a methodology to produce graded, strain-related injuries in cultured cells and evaluate their structural and functional response. This methodology is designed to determine the thresholds of injury, both structural and functional, to support developing assessments of brain injury.

Disclosures: **A. DiLeonardi:** None. **E.A. Matheis:** None. **K. Rafaels:** None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.12/DD8

Topic: C.10. Brain Injury and Trauma

Support: MOMRP Grant

Title: Blast exposure leads to accelerated brain aging in rats

Authors: ***P. ARUN**, F. ROSSETTI, D. WILDER, S. SAJJA, S. VANALBERT, Y. WANG, I. D. GIST, J. B. LONG

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Abstract: Blast-induced traumatic brain injury (bTBI) is one of the major causes of persistent disabilities in Service Members, and a history of bTBI has been identified as a primary risk factor for developing age-associated neurodegenerative diseases. Initial clinical observations using diffusion tensor imaging to evaluate military victims exposed to blast revealed that blast exposure causes a rapid age-related loss of white matter integrity in the brain. In the present study, using an advanced blast simulator (ABS) we have tested the effect of single and tightly coupled repeated blast exposures on aging of the rat brain. Anesthetized rats were exposed to either a single or 2 closely coupled blasts (19 psi peak total pressure, 4-5 msec duration) in the

ABS. Rats were euthanized and brains were collected at 24hr and 1 month post-blast to determine the changes in molecular and neuropathological markers of aging. Brain sections were prepared with senescence marker stain which measures senescence-associated- β -galactosidase activity in the cells. Real-time quantitative RT-PCR (qRT-PCR) was carried out to determine the differential expression of other protein markers of aging. Single and closely coupled repeated blast exposures resulted in significantly increased senescence marker staining in several neuroanatomical structures, including the hippocampus, auditory cortex, optical layer of the superior colliculus, thalamus and geniculate. The increases in senescence-associated- β -galactosidase activity were more pronounced at 1 month than at 24hr post-blast and were also greater after repeated than after single blast exposures. In addition, qRT-PCR analysis of brain homogenates indicated decreased mRNA levels of senescence marker protein 30 (SMP30) and increased mRNA levels of p21 (cyclin dependent kinase inhibitor 1A, CDKN1A). These findings are consistent with the earlier observations in veterans exposed to military blast and reveal that exposure to blast triggers accelerated aging of cells in the brain. It is noteworthy that the rapidly aging cells were not uniformly observed in the brain after blast exposure and were restricted to specific brain regions. The increased senescence observed in some of these affected brain structures may be implicated in several long-term sequelae after exposure to blast, including memory disruptions and impairments in auditory and ocular functions.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.13/DD9

Topic: C.10. Brain Injury and Trauma

Support: NINDS grant 1R01NS096143

Title: Neuronal membrane disruption persists chronically following diffuse brain injury in the rat

Authors: *A. D. LAFRENAYE, M. MARONE, M. HERNANDEZ
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Abstract: Neuronal membrane perturbation/disruption has been observed acutely following traumatic CNS injury, however, the time-course over which membrane disruption occurs and the molecular mechanisms involved in this pathology remain undefined. Therefore, we investigated the time course of neuronal membrane disruption for 4w following diffuse brain injury. Interestingly, alterations in cathepsin-B localization were previously seen acutely in membrane compromised neurons, therefore, cathepsin-B cellular localization was also assessed at more

chronic time points. To these ends, we utilized a central fluid percussion injury (CFPI) model in adult male rats paired with intraventricular infusions of cell-impermeable tracers administered at various time points (6h, 1d, 3d, 1w, 2w and 4w; $n \geq 4$ animals per group) following TBI or sham injury. Uptake of these tracers, indicative of membrane perturbation, was assessed via confocal microscopic analysis. Cell loss within 4w post-injury was quantified via hematoxylin and eosin analysis. To investigate the ongoing subcellular alterations occurring in sub-acutely membrane porated neurons, electron micrographs, labeled to detect the infused tracers, were assessed throughout the first month post-TBI. The localization of cathepsin-B within either membrane disrupted neurons or neurons with intact membranes was also evaluated using immunohistochemistry paired with semi-quantitative confocal image analysis. All assessments were done by investigators blinded to the group. Through these approaches we observed ongoing neuronal membrane perturbation in layers V and VI of the lateral neocortex at 6h, 2w and 4w post-TBI, however, no correlative cell loss was observed at any time. While some neurons displayed subcellular changes consistent with perturbation or cell death, the majority of neurons sustaining active membrane poration over the 1 month post-CFPI period appeared normal. Cathepsin-B localization was also observed from 1d to 4w post-CFPI with indications that both membrane disruption and cathepsin-B relocalization are linked to neuronal atrophy. These findings suggest that diffuse neuronal membrane perturbation has a prolonged pathogenesis following TBI and that cathepsin-B may play a role in the progression of this pathogenesis. Understanding the pathological progression of diffuse neuronal membrane disruption could lead to the development of novel therapeutics for the treatment of TBI patients.

Disclosures: A.D. Lafrenaye: None. M. Marone: None. M. Hernandez: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.14/DD10

Topic: C.10. Brain Injury and Trauma

Support: CDMRP/DOD AZ140064

Title: Assessing the role of tau upon cytoskeleton dynamics in hiPSC derived neurons during mechanical injury

Authors: *A. HOLDER¹, E. GUTIERREZ², A. DICKEY², M. PATINO², A. GROISMAN², L. GOLDSTEIN², A. ALMENAR-QUERALT², S. SHAH², R. CHAVES²

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Abstract: Traumatic brain injury (TBI) is a high risk factor for cognitive decline and dementia. The mechanisms leading to neurodegeneration following injury remain widely unknown. Disruptions in the neuronal microtubule cytoskeleton are hypothesized to lead to axonal morphological changes observed in animal models of TBI and in post-mortem brains of TBI patients. These axonal morphological changes, including wavy and swollen axons, may be exacerbated by the activity of Tau, a microtubule associated protein whose reduction and elimination has been shown to alleviate TBI-induced microtubule pathology in animal models. To elucidate Tau's role in injury induced cytoskeletal disruptions in human neurons, we first developed a microfluidic biomedical device to produce a sub lethal mechanical strain on human induced pluripotent stem cell (hiPSC)-derived neurons seeded on a flexible substrate, simulating the biomechanical loading neurons experience during TBI. We compared axon morphology in unstretched cells to those subjected to 50 stretch-release cycles at 24% strain. We found that mechanical loading results in immediate and transient morphological changes, including waves along the length of axons that mimic those found in post-mortem brains of individuals previously exposed to TBI. Axons aligned in the direction of stretch were most likely to display structural changes. Also, monitoring microtubule dynamics in these neurons demonstrated a transient cytoskeletal reorganization, in which axonal microtubule levels decreased and then returned towards pre-injury levels within 24 hours. To evaluate Tau dependence in injury-induced axonal pathology, we engineered a *MAPT* knockout hiPSC line by introducing a premature stop codon within exon 2 of the *MAPT* gene using CRISPR/Cas9 genome editing technology. Here, we compare axonal morphological changes and microtubule dynamics after injuring neurons derived from wild type and *MAPT* knockout hiPSC-derived neurons. Examining Tau's role in the cytoskeletal disturbances following injury might provide mechanistic insight into TBI induced neurodegeneration and may lay the groundwork in understanding how brain injury could ultimately lead to increased risk for Alzheimer's disease.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.15/DD11

Topic: C.10. Brain Injury and Trauma

Title: The effects of mechanical vibration on cellular health in differentiated neuroblastoma cells

Authors: *C. SHI¹, R. CHANG², D. LEONARDI¹

¹Bergen County Academies, Hackensack, NJ; ²Stevens Inst. of Technol., Hoboken, NJ

Abstract: The effects of mechanical impact forces on neurological health is a critical concern, likely due to issues of traumatic brain injury (TBI) in sports and brain damage stemming from the recent suspicion of “sonic terrorism.” The quantitative analysis and evaluation of such forces on brain tissue function is very difficult. To address this issue, this research proposes a novel approach of using a cellular model subjected to mechanical vibration for analysis. Here, neuron-like differentiated neuroblastoma cells were subjected to vibration at frequencies of 20, 200, 2000, and 20000 Hz for a period of 24 hours at constant amplitude. Cell proliferation and cytokine production, including inflammatory cytokines IL-6, IL-1 β , and TGF- β 1 and hypoxia-induced cytokine VEGF, was measured as response of the cells and indicators of cellular health after vibrational treatment. Cell proliferation was found to increase after 20, 200, and 20000 Hz treatments; ($p < 0.05$) and decrease after 2000 Hz treatment ($p < 0.05$). IL-6 expression was found to decrease after 200 and 20000 Hz treatments ($p < 0.01$) and increase after 20 and 2000 Hz treatments ($p < 0.01$). IL-1 β protein production was found to decrease after 20 Hz and increase after 200 Hz treatments ($p < 0.001$), while TGF- β 1 was found to decrease after 200 Hz treatment ($p < 0.001$). VEGF production was found to increase after 2000 Hz treatment and decrease after 20000 Hz treatment ($p < 0.05$). The results suggest that cell proliferation and cytokine production serve as a sensitive measure to external impact forces applied to the cells. It is shown that inflammatory and hypoxia-induced mechanisms are employed in cells exposed to vibration, and it is proposed that inflammatory mechanisms exhibit inhibitory “cross-talk” between IL-6 and IL-1 β signaling pathways at 20 and 200 Hz. Inflammatory and hypoxia-induced cytokine data suggest frequency-specific responses, which can be used not only to better understand the mechanism of vibration induced cellular damage, but also to unveil the cellular signaling processes.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.16/DD12

Topic: C.10. Brain Injury and Trauma

Support: Centre for international Mobility (CIMO)
Finnish Epilepsy Association
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Instrumentarium foundation
Maire Taposen foundation

Title: Chronically altered miRNA signature in the ipsilateral thalamus and perilesional cortex in rats with traumatic brain injury

Authors: *S. DAS GUPTA, N. VUOKILA, N. PUHAKKA, A. PITKÄNEN
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Abstract: Neuroinflammation is a long-lasting secondary injury mechanism that evolves in the brain for months after traumatic brain injury (TBI). MicroRNAs (miRNAs) have been identified as key regulators of neuroinflammation after CNS injuries.

Our objective was to identify an altered miRNA signature in the brain months after TBI. We hypothesized that chronically altered miRNAs play a role in modulating post-TBI neuroinflammation.

At 2 months post-TBI, adult male Sprague-Dawley rats (n=22) with experimental TBI underwent T2-w MRI, to identify perilesional cortical inflammation (n=13/22). At 3 months post-TBI, small RNA sequencing was performed on samples from ipsilateral thalamus and perilesional cortex of selected rats with the inflammatory endophenotype (n=6/13), and sham operated controls (n=6). Altered miRNAs were validated with droplet digital PCR (ddPCR). Target prediction for validated miRNAs was done with TargetScan 7.2, and only the targets present in our mRNA-Seq data with significantly opposite fold change (FC) to the miRNA expression (FDR<0.05) were selected for DAVID gene-Gene Ontology term enrichment analysis.

Small RNA-Seq identified dysregulation in 2 and 19 miRNAs, in the thalamus and cortex respectively (FDR<0.05). The 2 candidates from thalamus and the top 10 from cortex were selected for validation. In thalamus, elevated miR-146a-5p (FC=2.01, p<0.05) and miR-155-5p (FC=2.34, p<0.01) levels were validated after TBI as compared to controls. In cortex, elevated miR-375-3p (FC=3.44, p<0.01) and miR-211-5p (FC=1.45, p<0.05) levels were validated after TBI as compared to controls. For miR-146a and miR-155, 6% and 8% of predicted targets respectively were downregulated in our thalamus mRNA-Seq (FDR<0.05). Similarly, 7% of miR-375 and miR-211 targets were downregulated in cortex (FDR<0.05). Enrichment analysis revealed “Integral membrane component”, “ion channel” and “ion transport” as the top GO terms in thalamus, and “cytoplasm”, “transferase” and “protein stabilization” for cortex.

Our data indicate that both pro- (miR-155) and anti-inflammatory (miR-146a) miRNAs are elevated in the thalamus at a chronic time post-TBI. However, the role of the dysregulated miRNAs from cortex in neuroinflammation is not well known. Unlike expected, gene targets for the validated miRNAs that were present in our mRNA-Seq data appear to be regulating neurotransmission and post-translational protein modification rather than neuroinflammation. Further analysis is needed to identify if altered neurotransmission predisposes the endophenotype towards development of spontaneous seizures.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.17/DD13

Topic: C.10. Brain Injury and Trauma

Support: USUHS Grant HU0001-15-2-0024

Title: Alterations in amyloid beta peptide levels following subclinical blast overpressure exposure in a rodent model of traumatic brain injury

Authors: *S. L. CIARLONE^{1,2}, J. A. GOODRICH^{1,2}, C. W. GOFORTH^{1,3}, S. T. AHLERS¹, A. E. TSCHIFFELY¹

¹Neurotrauma, Naval Med. Res. Ctr., Silver Spring, MD; ²Henry M. Jackson Fndn., Bethesda, MD; ³Surgery, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Since 2000, nearly 350,000 service members have been diagnosed with traumatic brain injury (TBI), approximately 82% of which are classified as mild and often result from blast injury. Currently, the effects of a primary blast wave on the brain, as well as its underlying mechanisms, are poorly understood. Several proteins associated with neurodegenerative diseases accumulate in the brain following non-blast TBI (nbTBI), including amyloid precursor protein (APP) and its cleavage product amyloid beta (A β). However, the unique pathophysiologic features of blast compared to nbTBI merits further evaluation of A β processing and clearance. Our group recently demonstrated that a single low-intensity blast overpressure (BOP) exposure results in a reduction of A β protein in the rodent cortex. Here, our goal was to investigate the acute effects of BOP on temporal A β clearance following various intensities of blast in order to elucidate a mechanism underlying aberrant A β regulation post-exposure. We hypothesized that low-level blast would result in both acute and chronic differential regulation of A β in the brain, CSF, and serum post-BOP exposure, and that the underlying mechanism of dysregulation would be associated with clearance through the CSF and serum rather than via amyloidogenic processing of APP. We exposed anesthetized male Long-Evans rats (n = 10/group) to mild and moderate blast pressure to determine the effect of varying blast intensities on A β clearance. Rats were humanely euthanized at predetermined acute and chronic time points post-BOP in order to simultaneously evaluate the effects of blast intensity and temporal aspects of A β metabolism in various tissues and biospecimens. Preliminary data demonstrated acute reductions in cortical and hippocampal A β _{42/40} at lower blast intensities associated with subclinical blast exposure (5 and 11 psi), as well as dysregulation in both CSF and serum 24 hours post-BOP compared to moderate exposure (18 psi) and sham controls. Moreover, although APP increased following blast, we measured no significant alterations in components of amyloidogenic processing, including β - and γ -secretases. These data suggest a rapid A β clearance from the brain following

blast, which may indicate an altered glymphatic system response. Previous studies inhibiting A β production improved outcomes following nbTBI in rats; however, our work suggests clearance pathways may be useful therapeutic targets for treating acute blast TBI injuries. Future research should further explore the complex temporal interaction of blast injury and A β clearance to ultimately guide the development of novel diagnostic and therapeutic approaches.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

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Program #/Poster #: 056.18/DD14

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS085568
NIH Grant NS091585
VA National Merit Grant RX000666
VA National Merit Grant RX001473

Title: Long-term pericyte response following traumatic brain injury in mice

Authors: *M. R. MCCRARY¹, K. K. JESSON², J. Y. ZHANG², X. GU², S. YU⁴, L. WEI³
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Abstract: Traumatic brain injury (TBI) is a leading cause of mortality and morbidity and contributes to about 30% of all injury deaths in the US. Following TBI, the cerebral vasculature incurs both direct and secondary damage. Vascular regeneration entails a series of complex events including angiogenesis, arteriogenesis, and pericyte recruitment. In the brain, these events are intimately tied to functional recovery. Pericytes play an integral role in the acute response to TBI. Both vessel-associated and non-vessel-associated pericytes are involved in regeneration. However, the pericyte response long-term after traumatic brain injury is understudied. In the present investigation, we studied the pericyte response weeks after injury. Adult transgenic mice expressing α -SMA-GFP were subjected to controlled cortical impact stereotactically directed to the sensorimotor cortex. BrdU was administered daily after injury to monitor for newly formed cells. TBI animals were sacrificed 2, 3, 5, and 8 weeks after injury for histologic inspection of pericytes. Images of stained slides were analyzed using ImageJ under double-blind conditions. Tissue was isolated from the peri-contusion region and the contralateral cortex. Western blot analyses of tissue collected from the injury region suggests that angiogenic and pericyte-related factors such as VEGF, EPO-R, and TNF- α remain elevated in the peri-contusion region weeks after

injury. Staining revealed that the pericyte markers Kir6.1 and PDGFR- β were co-expressed in most α -SMA+ cells following injury. At 2 weeks after TBI, amoeboid appearing α -SMA+ cells not associated with vasculature were noted within the peri-contusional astrocytic scar. Cells with these features were also found in the subventricular zone. The number of vessel-associated α -SMA+ cells continued to increase over 8 weeks. Taken together, these data suggest that pericytes play varying and prolonged roles in the cellular response to traumatic brain injury. Future studies will elucidate the complexities of the brain pericyte response and its implication for the treatment of brain injury.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.19/DD15

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant GM110674

Title: Neonatal disruption of PSD-95 PDZ domain-mediated protein-protein interactions alters dendritic spine morphology, long-term potentiation, and causes deficits in learning and memory in mice

Authors: M. L. SCHAEFER, M. WANG, P. J. PEREZ, J. XU, C. GRAY, *R. A. JOHNS
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Abstract: *Background:* It has been reported that millions of infants and children receive anesthesia each year. Early exposure to procedures requiring anesthesia is a significant risk factor for later development of learning disabilities and disorders of attention and anxiety. In animal studies, newborns exposed to anesthetic agents develop neurodegenerative changes in multiple areas of the brain associated with long-term deficits in learning and memory. It is well established that inhibiting NMDA receptor signaling during development can lead to changes in synaptogenesis and neuronal circuit formation. Given that PSD-95 interacts with NMDA receptor, promotes synaptogenesis, and that multi-innervated spine formation is specifically prevented by deletion of the PSD-95 PDZ2 domain, we investigated disruption of PSD-95 PDZ2 domain interactions and downstream signaling as a potential mechanism for early anesthetic exposure-produced long-term cognitive impairment.

Methods and Results: Exposure of Postnatal day 7 (PND7) mice to 1.5% isoflurane for 4 hr or 8 mg/kg PDZ2 mimetic peptide causes abnormalities in spine morphological development as seen by a reduction in the spine marker Drebrin and the population of long thin spines at PND21.

With longer recovery a reduction in ‘mature’ mushroom spines was detected at PND50. No detectable levels of apoptosis were observed by Western blot for cleaved caspase 3 or TUNEL in our exposure paradigm. Electrophysiology studies indicate an impairment in the expression of LTP at PND21 that resolves by PND50. Results from acute and chronic recognition memory tests indicate that both isoflurane and PDZ2 mimetic peptide impair memory. Contextual fear memory tested at PND56 showed impairment in mice exposed to isoflurane and the PDZ2 mimetic peptide. The loss of mushroom spines (but not loss of long thin spines), impairment in acute recognition memory, and LTP could be prevented by introduction of a nitric oxide donor. *Conclusion:* Our data support previous work in rodents showing that neonatal isoflurane exposure causes both acute and long-term synaptic changes leading to learning and memory deficits. Specifically disrupting PSD-95 PDZ2 domain-mediated protein-protein interactions *in vivo* with PDZ2 mimetic peptides also impairs synaptic development and plasticity and causes acute and chronic learning and memory deficits. Introduction of a nitric oxide donor prevents isoflurane and peptide inhibitor induced impairment in recognition memory and LTP further implicating the PSD-95/NMDAR/nNOS pathway in playing a role in isoflurane induced cognitive impairment.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

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Topic: C.10. Brain Injury and Trauma

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Title: TBI-activated AEP contributes to AD onset through C/EBP β activation

Authors: *Z. WU^{1,2}, X. GU¹, X. LIU¹, L. WEI¹, S. YU¹, L. CHENG², K. YE¹

¹Emory Univ. Sch. of Med., Atlanta, GA; ²Tongji Hosp. Affiliated to Tongji Univ. Sch. of Med., Shanghai, China

Abstract: Background: TBI is one of the most consistent candidates for initiating the molecular cascades that result in Alzheimer’s disease (AD). δ -secretase, also known as asparagine

endopeptidase (AEP) or legumain, is a lysosomal cysteine proteinase activated in acid pH environment and cleaves substrate after asparagine residues. After activation, AEP can directly cleave Tau at N255 and N368. Moreover, the expression of AEP is controlled by a transcriptional factor CCAAT/Enhancer Binding Protein Beta (C/EBP β). We hypothesize that TBI induces AEP upregulation and enhances its enzymatic activity via C/EBP β activation, which leads to elevated APP and Tau cleavage and AD pathogenesis. **Methods:** TBI mice was established by control cortical injury model. The behavioral (water maze, fear condition test), pathological (hyperphosphorylation Tau, A β , neuroinflammation and neuronal death), morphological (Golgi staining and EM exam for CA1 neuron) and molecular (WB, qPCR, AEP activity test) outcomes of AEP $^{+/+}$ and AEP $^{-/-}$ mice after TBI at were compared at short-term (7d) and long-term (6m and 12m). Meanwhile, same comparisons were also made between 3xTg \times AEP $^{+/+}$ and 3xTg \times AEP $^{-/-}$, as well as 3xTg \times C/EBP $\beta^{+/+}$ and 3xTg \times C/EBP $\beta^{+/-}$. In vitro model included hypoxia and serum depletion in either HEK293T cells or rat cortical neuron. In addition, an organotypic culture of mouse hippocampus slice was injured by a weight drop model. Specific Tau N368 antibody was administrated for blocking the spreading of Tauopathy after adding the TBI brain lysate into neuron. **Results:** TBI stimulates AEP upregulation and activation at 7 days after injury, and the AD-related biological changes show up. Not only in the animal model *in vivo*, but also in the *in vitro* model, AEP can be activated by traumatic injury. In the wild-type mice at a chronic stage after TBI, three of four major AD pathologies are found, although THS staining is negative. Mice lacking of AEP expression have less severe behavior changes and better biological and pathological outcomes. Compared to 3xTg \times C/EBP $\beta^{+/+}$ mice, the 3xTg \times C/EBP $\beta^{+/-}$ mice demonstrated significant less severity of TBI-induced AD pathologies. As the transcriptional factor of AEP, Tau, APP, the activation of C/EBP β enhances the accumulation of the material that are required for AD onset. Furthermore, the spreading of Tau N368 through neuronal axon, but not the dendrite. Moreover, The Tau hyperphosphorylation and aggregation were fully blocked by Tau N368 antibodies *in vitro*. **Conclusions:** As a AD-related risk factor, TBI induces AEP activation in a time-dependent manner. TBI activates the transcription factor C/EBP β that mediates AEP upregulation and AD pathologies.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.21/DD17

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant F31 NS105451-01A1

Title: Glial and fibrotic differences in traumatic brain injury and spinal cord injury with and without immunomodulation

Authors: *S. SHARMA, J. G. COOPER, S. JEONG, I. IFERGAN, S. MILLER, J. A. KESSLER
Northwestern Univ., Chicago, IL

Abstract: Traumatic brain injury (TBI) and spinal cord injury (SCI) cause a primary wave of cell death from the initial impact and a subacute to chronic cell damage and parenchymal remodeling which is significantly contributed by the neuroinflammatory and scarring responses. In this study, we present the mechanistic differences between TBI and SCI natively and in response to therapeutic ablation of hematogenous monocytes and saline/vehicle control treatments. Studies employing immunosuppression as a means to modulate this secondary damage have given conflicting results with respect to behavioral recovery and anatomic/lesion architecture in animal models of traumatic and contusive CNS injuries. A main factor for these discrepancies is the use of pan-immunosuppressive treatments such as clodronate liposomes and a lack of a targeted ablation of pro-inflammatory cells at acute/subacute injury time-points. From our previous studies employing biodegradable poly(lactic-co-glycolic)acid (PLGA-IMPs), which selectively ablate hematogenous monocytes to specifically attenuate the proinflammatory injury response, we have shown in a previous publication (Jeong et al. 2017) an improvement in behavior (as assessed by the Basso Mouse Scale) and anatomy in mouse model of contusive SCI (reduced fibrotic scarring). Using mouse contusive-SCI and controlled cortical impact TBI (CCI-TBI) paradigms, we show clear differences in basic pathophysiology including a lack of fibrosis in TBI compared to fibronectin laden SCI lesion cores, speedier recovery in mouse CCI-TBI, and cavitory tissue architecture in TBI. These differences are accentuated following PLGA-IMP treatment which changes the long-term fibrotic scar without changing astrocytic responses in SCI whereas monocyte ablation after CCI-TBI changes astrocytic responses drastically. In blinded studies with saline/vehicle, PLGA-IMP, and sham injuries using 8-10 week C57BL/6 male and female mice, these results have been replicated. Appreciating the difference in acute astrocytic responses after contusive injuries in the brain and spinal cord supports the hypotheses that different mechanisms must be manipulated to apply acute treatment modalities for these superficially similar but truly very different injuries.

Disclosures: S. Sharma: None. J.G. Cooper: None. S. Jeong: None. I. Ifergan: None. S. Miller: None. J.A. Kessler: None.

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.22/DD18

Topic: C.10. Brain Injury and Trauma

Support: AA017991
AA07680
AA022448

Title: Targeting gephyrin for treatment of anxiety

Authors: Y. SHEN¹, A.-K. LINDEMEYER², A. S. SHAO², X. M. SHAO³, D. L. DAVIES⁴, R. W. OLSEN², *J. LIANG⁴

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Abstract: Anxiety disorders are the most common mental illness in the United States with many patients exhibiting treatment-resistance or substantial side effects to available pharmacotherapies. As such, new treatment strategies are critically needed. A promising new treatment approach that we are proposing involves the modulation of gephyrin, an assembly protein that anchors and clusters inhibitory neurotransmitter receptors, including GABA_A receptors (GABA_AR) to the postsynaptic cytoskeleton. In support of this hypothesis, work from our group suggest an association between decreases in neuronal gephyrin, altered responsiveness of extra- and post-synaptic GABA_ARs and increases in behavioral anxiety levels. Collectively, this work, suggests that increasing gephyrin levels within limbic circuits can restore impaired GABA_AR physiology and ameliorate anxiety behavior. The current study tests the hypothesis that gephyrin represents a novel treatment target for anxiety. We tested the effects of dihydromyricetin (DHM; a flavonoid purified from herb *Hovenia*) using a social isolation mouse anxiety model. We found that in mice, singly housing resulted in a decrease in gephyrin levels in the hippocampus and impairment in GABA_AR-mediated neurotransmission in dentate gyrus granule cells (DGCs). Notably, DHM (2 mg/kg, gavage, once per day for 3 weeks) antagonized the reduction in gephyrin levels and counteracted the GABAergic transmission impairment. Behaviorally, DHM reversed the anxiety levels in mice induced by social isolation. Overall, this work illustrates the importance of the gephyrin-GABA_AR pathway as a novel mechanism and treatment target for the management of anxiety disorders. Support: AA017991, AA07680, AA022448.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.23/EE1

Topic: C.10. Brain Injury and Trauma

Support: R42MH097377
17GRNT33700108

Title: Molecular mechanism that triggers synaptic remodeling following axon injury

Authors: ***T. NAGENDRAN**^{1,2}, A. M. TAYLOR^{1,2,3}

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Abstract: Injury of central nervous system (CNS) nerve tracts remodels circuitry through dendritic spine loss and hyper-excitability, thus influencing recovery. Due to the complexity of the CNS, a mechanistic understanding of injury-induced synaptic remodeling remains unclear. Using microfluidic chambers to separate and injure distal axons, we show that axotomy causes retrograde dendritic spine loss at directly injured pyramidal neurons followed by retrograde presynaptic hyper-excitability. Mirroring this *in vitro* result, directly injured corticospinal neurons *in vivo* also exhibit a specific increase in spiking following axon injury. Next we show that blocking local activity, using TTX and low calcium buffer, at the site of injury prevented dendritic spine loss. Similarly, applying a reversible transcription inhibitor to somata for 1 h at the time of injury prevented axotomy induced dendritic spine loss. These results suggest that activity at the site of injury triggers gene transcription and regulate dendritic spine loss. Thus we hypothesize that sodium influx locally at the site of injury might be a priming factor for triggering retrograde injury signal, which regulates gene transcription and dendritic spine loss. Together our findings suggest that activity at the site of spinal cord injury can trigger axon-to-soma signaling inducing transcription dependent synaptic reorganization and remodeling in the brain.

Disclosures: **T. Nagendran:** None. **A.M. Taylor:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A.M.T. is an inventor of the microfluidic chamber/chip (US 7419822 B2) and is a member of Xona Microfluidics, LLC..

Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.24/EE2

Topic: C.10. Brain Injury and Trauma

Support: VA Competitive Pilot Project Fund
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1-F32NS090748
The Pittsburgh Foundation
VAI01RX001127

Title: Traumatic brain injury reduces heat shock factor 1 abundance in the hippocampus for weeks post-injury

Authors: *C. DIXON, J. HENCHIR, Y. LI, X. MA, S. CULVER, C. BERKEY, S. W. CARLSON
Neurosurg., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Traumatic brain injury (TBI) impairs neuronal function which can culminate in lasting cognitive dysfunction. Heat shock proteins are molecular chaperones that are induced under a variety of pathological conditions, including ischemia, neurodegenerative disease, epilepsy, and trauma. Activation of the heat shock protein system has been shown to play an important role in injury response and a therapeutic target for pharmacological intervention to promote neuroprotection and recovery of neurobehavioral function after TBI. Heat shock factor 1 (HSF1) is an important transcriptional factor in the regulation of the heat shock protein system. The effects of TBI on HSF1 are poorly understood. The goal of this study was to evaluate the effect of TBI on HSF1 abundance at multiple time points post-injury. To achieve this, male Sprague-Dawley rats received controlled cortical impact (CCI; 2.7mm) or sham injury and tissue collected at 1, 7 or 14 days post-injury. Immunohistochemical assessment revealed reduced hippocampal immunoreactivity in CA1, CA3, and granular layer of the dentate gyrus at 1, 7 and 14 days post-injury (n=6/group). Immunoblot analysis of revealed a reduction in hippocampal HSF1 abundance of CCI-injured rats compared to sham control rats at 1 day (p<0.05, Student's t-test) and 7 days (p<0.001, Student's t-test) post-injury. CCI resulted in a robust reduction in hippocampal HSF1 abundance. Additional studies are warranted to evaluate additional time points and brain regions to gain insight into the effect of TBI on HSF1 and optimal therapeutic interventions for activation of the heat shock protein system.

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Poster

056. Brain Injury and Trauma: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 056.25/EE3

Topic: C.10. Brain Injury and Trauma

Title: Enhanced temporal resolution of *in vitro* post-impact neural network oscillation frequency reductions using cross correlation analysis

Authors: *E. A. ROGERS¹, N. SURI², G. W. GROSS²

¹Biol., Ctr. For Network Neurosci., Denton, TX; ²Dept Biolog Sci., Univ. North Texas, Denton, TX

Abstract: Cross correlation (CC) analysis of activity relationships between cortical cells in primary neuronal cell cultures growing on microelectrode arrays (MEAs) revealed oscillations in the range of 1.5 to 3.0 Hz (general Delta range) in the native state without chemical induction and at the biological temperature of 37°C. Blocking inhibitory synapses with 40uM bicuculline decreased the frequency to a range of 0.5 to 1 Hz.

We have previously shown [1,2] that cellular sub-lethal impacts can modulate these oscillations. Application of a ballistic impulse generator and neuronal networks on MEAs has allowed simultaneous morphological and multichannel electrophysiological monitoring over long (~2 days) pre and post-impact time periods. Impact trauma results in reproducible changes in spontaneous activity that can be described in terms of two phases: An initial 5-15 min activity depression and subsequent return to almost reference in approx. 1 hour (Phase 1), followed by a slow decrease to persistent levels 30 to 40% below reference (Phase 2) that last at least 48 hours. CC analysis of pre (reference) and post impact network activity from wave shape identified units show alterations of spike distribution profiles and an average 20% decrease in network oscillations during the first 20 min of Phase 1. Analyzing this period with six consecutive 200 sec data segments reveals a reproducible (n=8) recovery in oscillations at an average rate of 0.05 Hz/min to near-reference values. Control measurements over multiple reference periods do not show significant oscillation variation (n=5). This gradual, reproducible spontaneous recovery can be used as a quantitative measure for evaluations of the efficacy of physical, chemical, and pharmacological interventions. Altered oscillations measured in patients after TBI have been reported and are beginning to be used as a tool for diagnosing brain injury [3]. These results may provide a unifying metric between *in vitro* and *in vivo* brain injury studies.

[1] Rogers EA, Gross GW (2017) Society for Neuroscience Abstract #2934.

[2] Rogers EA, Gross GW (2018) Manuscript submitted to Scientific Reports, under review.

[3] Huang et al. (2012) Neuroimage 61: 1067-82.

Disclosures: E.A. Rogers: None. N. Suri: None. G.W. Gross: None.

Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.01/EE4

Topic: D.02. Somatosensation

Support: FEDER - Fundo Europeu de Desenvolvimento Regional funds through the COMPETE 2020 - Operacional Programme for Competitiveness and Internationalization (POCI), Portugal 2020
FCTPTDC/NEU-NMC/1259/2014 (POCI-01-0145-FEDER-016588)
Hungarian Brain Research Program (KTIA_NAP_ 13-2-2014-0005)

Title: Nociceptive trigeminal afferent input to cervical lamina I neurons

Authors: L. L. LUZ¹, P. SZUCS², *B. V. SAFRONOV³

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Abstract: The upper cervical cord is a part of the trigeminocervical complex that receives primary afferent inputs from the cervical somatic structures and cranial meninges. Cervical lamina I neurons processing and relaying these inputs are considered as the neural substrates of primary headache syndrome, e.g. migraine. Organization of the 'long-range' nociceptive afferent inputs from the trigeminal nerve to the cervical lamina I neurons is poorly understood. Here we developed a new preparation of the isolated trigeminocervical complex and did tight-seal recordings of the long-range nociceptive trigeminal inputs to the spinal lamina I neurons residing in the segments C1-C4. For recordings, the neurons were visualised using oblique LED illumination technique. Two-thirds of recorded lamina I neurons showed intrinsic rhythmic discharge pattern. The monosynaptic inputs from the trigeminal A δ and C afferents were recorded in the spinal lamina I neurons in the C1, C2 and, although to lesser degree, C3-C4 segments. These observations were supported by our labelling experiments showing that thin trigeminal afferents project to the superficial dorsal horn of several cervical segments. In conclusion, our study demonstrates that spinal cervical lamina I neurons receive strong direct inputs from the nociceptive trigeminal afferents.

Disclosures: L.L. Luz: None. P. Szucs: None. B.V. Safronov: None.

Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.02/EE5

Topic: D.03. Somatosensation: Pain

Title: Implication of trigeminal neural pathways in blue light photosensitivity

Authors: *V. MAREK^{1,2}, A. DENOYER^{2,3,4}, T. VILLETTE¹, A. CHARBONNIER², C. BAUDOIN^{2,3,5}, A. RÉAUX - LE GOAZIGO², S. MÉLIK PARSADANIANTZ²

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Paris, France; ³Ctr. Hospitalier Natl. d'Ophtalmologie des Quinze-Vingts, Paris, France; ⁴CHU Robert Debré, Univ. Reims Champagne-Ardenne, Reims, France; ⁵Versailles-Saint-Quentin-en-Yvelines Univ., Versailles, France

Abstract: Photophobia and associated ocular pain frequently accompany various neuro-ophthalmic disorders. However, their pathophysiology is still not clear. We investigated *in vivo* the neurological origin of photophobic behavior in mice exposed to blue light and identified the corresponding neuroinflammatory processes in the trigeminal pathways. Since cornea-innervating afferents of the trigeminal ganglion (TG) are in direct contact with ambient light, we studied *in vitro* the phototoxic processes in primary culture of trigeminal neurons. Adult male C57BL/6J mice were exposed for 3 hours either to blue (400-500 nm) or to orange (530-710 nm) light (6 mW/cm²). For behavioural tests, mice could freely move between darkened and illuminated parts of the cage; photosensitivity was assessed by time spent in each part. Bilateral treatments were performed: topical instillation of atropine, pilocarpine or oxibuprocaine and intravitreal injection of lidocaine. For immunohistological analysis, mice were restrained in the illuminated part of the cage and immediately sacrificed after the end of exposure; TG, brainstem and retina were dissected out. *In vitro*, dissociated TG were cultured for 10 days (with or without antimetabolic treatment on the 3rd day) and illuminated for 3 hours by 10 nm wavebands (1.1 mW/cm²) centred at 410, 440, 480, 510 and 630 nm. Control cultures were kept in the dark. Light-induced cytotoxicity was assessed by cell viability and reactive oxygen species rates.

Non-treated mice were highly aversive to blue but not to orange light. None of the applied instillations impacted the time spent under blue light as compared to control PBS instillation. Surprisingly, PBS-instilled mice spent significantly less time under blue light than non-treated mice. This effect did not take place for orange exposure. Lidocaine injection did not change the behaviour of blue-exposed mice; however, it significantly decreased the time under light for orange exposure. In blue-illuminated mice, we observed increased immunoreactivities of FOS and Iba1 in the sensory complex of trigeminal subnucleus, ATF3 in the TG and GFAP in the retina. *In vitro*, at the end of light exposure, the viability of TG cells significantly decreased at 410 nm. This decline was accompanied by morphological changes and H₂O₂ over-production. In glial cells, a significant increase in mitochondrial O₂⁻ rate was detected.

Our results suggest that besides the spectrally independent photosensitivity mediated by visual retinal photoreceptors, wavelength-dependent light aversion might implicate pain-related trigeminal pathways, namely trigeminal ganglion and subnucleus neuronal and glial cell population.

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Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.03/EE6

Topic: D.03. Somatosensation: Pain

Support: NRF-2017R1A5A2015391

Title: Expression of vesicular glutamate transporter 1 (VGLUT1) and VGLUT2 in the axons and somata of the rat trigeminal primary sensory neurons in the normal condition and following inflammation

Authors: Y. CHO, J. BAE, H. HAN, *Y. BAE

Sch. of Dentistry, Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: Informations on the expression of vesicular glutamate transporter (VGLUT) in the axons and somata of the primary sensory neurons may help understand glutamate signaling mechanism associated with transmission of various sensory informations. This study, in order to elucidate type of VGLUTs and axons associated with craniofacial acute and inflammatory pain, examined expression of VGLUT1 and VGLUT2 in the rat trigeminal ganglion and peripheral sensory root in the normal condition and following CFA-induced inflammation by behavioral assay, light- and electron-microscopic immunohistochemistry and quantitative analysis. In normal rats, VGLUT1 was expressed mostly in the medium- and large-sized neurons whereas VGLUT2 was expressed mostly in the small- and medium-sized neurons. Most of the VGLUT1+ (71.8%) and VGLUT2+ (97.3%) axons were unmyelinated and small myelinated ($< 20 \mu\text{m}^2$ in cross-sectional area, equivalent to $A\delta$ fiber size). A large number of VGLUT1+ (28.2%), but few VGLUT2+ (2.7%) axons were large myelinated. Fractions of VGLUT1+ and VGLUT2+ unmyelinated axons of all examined axons were increased significantly whereas fractions of VGLUT1+ and VGLUT2+ small and large ($>20 \mu\text{m}^2$ in cross-sectional area, equivalent to $A\beta$ fiber size) myelinated axons were not changed when thermal hypersensitivity was developed following CFA-induced inflammation compared to control. These findings suggest that VGLUT1- and VGLUT2 are involved in the acute pain associated glutamate signaling and VGLUT1- and VGLUT2 in the unmyelinated fiber are involved in the inflammatory pain associated glutamate signaling.

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Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.04/EE7

Topic: D.03. Somatosensation: Pain

Support: SFB 1158

Title: Functional and anatomical interaction of olfactory and trigeminal signaling

Authors: M. MAURER¹, N. PAPOTTO², *M. SCHMELZ³, S. FRINGS², R. CARR¹
¹Exp. Pain Res., Heidelberg Univ., Mannheim, Germany; ²Ctr. for Organismal Studies, Heidelberg Univ., Heidelberg, Germany; ³Heidelberg Univ., Mannheim, Germany

Abstract: Within the nasal mucosa, chemosensitive trigeminal afferents reside in parallel with the olfactory system. Conventionally this trigeminal innervation is thought to guard against irritants through initiation of protective reflexes. However, human psychophysical studies suggest that the olfactory and somatosensory trigeminal systems may interact at the level of perception. In people, odor perception is attenuated by co-application of irritants while olfactory co-stimulation can modulate nasal nociception. However, the sites and mechanisms underlying olfactory and trigeminal interaction remain unknown. To address this question, we probed the anatomical and functional basis of olfactory-trigeminal cross talk in mice. To assess the behavioral implications of a consumption preference test, mice allowed to drink freely from either of two bottles developed an aversion ($p=0.009$) to water surrounded by the volatile TRPV1 irritant cyclohexanol (CYC). While the pure odorant phenyl ethyl alcohol (PEA) did not affect water consumption, its combination with CYC reduced the aversion. The possibility that the cross talk between olfactory and trigeminal systems occurred in the nose was assessed by performing electrophysiological recordings from individual trigeminal afferents innervating the nasal mucosa. PEA neither evoked activity nor modulated electrically-evoked signals in six single C-fibres innervating the nasal epithelium. In contrast, action potential activity was induced by CYC (1%, $n=11$), the TRPA1 agonist allyl isothiocyanate (AIC) (20 μM , $n=6$) and the TRPM8 agonist menthol (1 mM, $n=9$). The effect of pure olfactory stimulation was examined in mice expressing channel rhodopsin exclusively in olfactory sensory neurons OMP-ChR2-EYFP. Blue light stimulation (470 nm) evoked large electro-olfactogram signals from the olfactory epithelium, confirming optical activation of olfactory sensory neurons (OSNs). However, optogenetic OSN activation had no discernible effect on the excitability of single trigeminal C-fibres ($n=10$) in the olfactory epithelium. SNStdTomato and TRPM8eGFP mouse reporter lines were used to map trigeminal afferent projections within the caudal spinal trigeminal nucleus (Sp5) and C-fos labelling was used to determine activity in segmental lamina I and V neurons in response to intranasal AIC. C-fos signal was not observed after PEA

application. Our current data suggest that cross-modal interaction between nociceptive and olfactory signals does not reside in the nose. Further investigations are still ongoing to conclude about the spinal trigeminal nucleus.

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Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.05/EE8

Topic: D.03. Somatosensation: Pain

Support: NIH Grant DE018661
NIH Grant DE023090

Title: Comparison of orofacial cold sensitivity between male and female rats following infraorbital nerve chronic constrictive injury and oxaliplatin treatment

Authors: *F. EROL, J. LING, J. GU
Anesthesiol., Univ. Of Alabama At Birmingham, Birmingham, AL

Abstract: Sex differences in pain have been seen clinically and also observed in some animal models. We have previously shown with male rats that cold sensitivity in orofacial regions became increased to result in cold allodynia and hyperalgesia in animals following infraorbital nerve chronic constrictive injury (ION-CCI) and oxaliplatin treatment. In the present study, we aimed to evaluate whether male and female rats vary in their responses to the cold stimulation following ION-CCI and oxaliplatin treatment. We created rat models of ION-CCI and oxaliplatin-induced neuropathic pain in both males and females. Cold-sensitivity in orofacial regions was determined using the thermal orofacial operant test, which was designed to employ a reward-conflict paradigm with sweetened milk as a reward and cold temperatures as a potential painful stimulus. At the temperatures of 12°C and 5°C, ION-CCI groups of both male and female rats showed significantly higher cold sensitivity in comparison with their sham control groups. At the temperatures of 17°C and 24°C, female ION-CCI group displayed heightened cold sensitivity compared to their female sham group. In contrast, at these two temperatures male ION-CCI rats did not show significantly increases in cold sensitivity. For trigeminal neuropathy induced by oxaliplatin, female oxaliplatin-treated group also exhibited signs of cold hypersensitivity in comparison with their female control group treated with saline. The potential sex differences in orofacial cold sensitivity of oxaliplatin-treated animals will be quantitatively studied. Taken together, sex differences in cold sensitivity may be recapitulated with our rat

models of trigeminal neuropathy. This may provide a useful behavioral assessment for further studying mechanisms underlying the sex differences in trigeminal neuropathic pain.

Disclosures: F. Erol: None. J. Ling: None. J. Gu: None.

Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.06/EE9

Topic: D.03. Somatosensation: Pain

Title: Peripheral neurons invade oral cancer and drive oral carcinogenesis and pain

Authors: *N. N. SCHEFF¹, R. KLARES, III¹, J. W. QUAN¹, R. LAM¹, Z. R. CONLEY², B. E. AOUIZERAT¹, B. L. SCHMIDT¹

¹Bluestone Ctr. for Clin. Res., ²Col. of Dent., New York Univ., New York, NY

Abstract: The impact of sensory neurons on carcinogenesis is an understudied process in oral cancer. We used a preclinical mouse model and bioinformatics to study the reciprocal interaction of sensory neurons and oral cancer. We observed increased PGP9.5+ neuronal fiber density in the cancer microenvironment using high-resolution microscopy in a tongue oral cancer xenograft mouse model. *In vitro* we measured a $44.6 \pm 1.14\%$ increase in trigeminal neuron sprouting after 48 hour exposure to conditioned media from the human oral cancer cell line, HSC-3, compared to conditioned media from the dysplastic cell line (DOK) and the non-tumorigenic cell line, HaCaT. We tested the impact of peripheral nerves on tumor growth using a hindpaw oral cancer xenograft mouse model. Mice that received a sciatic nerve axotomy one week prior to HSC-3 inoculation developed significantly smaller tumors ($28.2 \pm 6.6\%$ of total paw area) compared to mice that received sham surgery ($50.7 \pm 2.48\%$). These data suggest that oral cancer induces sprouting of peripheral neurons and that this innervation drives oral cancer growth. We also previously demonstrated that HSC-3 produces more nociception than DOK or HaCaT in an oral cancer mouse model. To identify candidate genes in oral cancer that are involved in pain and initiate axonal sprouting, we utilized publically available oral cancer cell line gene expression data from the National Center for Biotechnology Information Gene Expression Omnibus (GEO). Gene co-expression network analysis of 5 cell lines for which we previously characterized nociceptive properties (nociceptive: HSC-3, SCC4, SCC9; non-nociceptive: DOK, HaCaT) identified 6 modules (*i.e.*, sets of co-expressed genes) associated with functional pain. Two modules featured perturbed pathways related to axon guidance, including sprouting. The axon guidance pathway included 3 differentially expressed semaphorin genes (*i.e.*, *SEMA4B*, *SEMA6A*, *SEMA7A*; t-test, all $p < 0.05$). We confirmed that the expression of *SEMA7A* is 3.5-fold higher in nociceptive oral cancer cell lines as compared to non-nociceptive cell lines. We also found that mouse trigeminal neurons express the semaphorin 7A protein target receptor, plexin

C1 (*Plxnc1*) and that there is a 2.5-fold increase in *Plxnc1* mRNA expression in trigeminal ganglia from mice with tongue oral cancer xenograft compared to control mice. Together, these data suggest a role for semaphorin 7A/plexin C1 signaling in neuronal sprouting into the oral cancer microenvironment leading to oral carcinogenesis and oral cancer pain. Understanding nerve-cancer interaction may yield novel therapeutic strategies to treat oral cancer and oral cancer pain.

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Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.07/EE10

Topic: D.03. Somatosensation: Pain

Support: NIDCR R01 DE026806 (Schmidt)

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NIDCR R03 DE027777 (Ye)

Title: Epidermal growth factor receptor (EGFR) signaling in the peripheral nervous system contributes to oral cancer pain

Authors: E. SALVO, R. VEERAMACHANENI, K. SINGH, D. ALBERTSON, B. SCHMIDT, *Y. YE

New York Univ., New York, NY

Abstract: Oral cancer patients experience function related pain that increases with disease progression and is not well managed. A role for activation of EGFR signaling in sensory neurons has been demonstrated with regard to neuropathic pain and hyperalgesic priming (a prolonged hypersensitized pain state following an acute inflammatory insult). To determine whether EGFR expressed in the peripheral nervous system (*i.e.*, sensory neurons and Schwann cells) contributes to oral cancer pain, we established that oral cancer cells are a potential source of EGFR ligands for activation of EGFR signaling in sensory neurons and Schwann cells. Activation of EGFR is common in oral cancers, occurring in more than 80% of invasive oral cancers. Oral cancer cells express EGFR ligands, including EGF, TGF- α , epiregulin, and amphiregulin. The oral cancer cells also express high mRNA levels of *ADAM17*, a disintegrin and metalloprotease that regulates the bioavailability of EGFR ligands, compared to non-tumorigenic skin keratinocytes (HaCaT). Moreover, we find that amphiregulin protein levels are elevated in the saliva of oral cancer patients with pain (N=7) compared to healthy, pain-free subjects (N=8, $P<0.05$). To investigate whether EGFR signaling is involved in communication between oral cancer cells and

Schwann cells, we determined that Schwann cells become more migratory and proliferative (characteristics of an activated phenotype) following exposure to oral cancer cells compared to exposure to dysplastic oral keratinocytes (DOK, $P<0.05$). Cancer exposed Schwann cells expressed higher levels of *EGFR* mRNA compared to the media control ($P<0.05$) and Schwann cell migration could be inhibited by Cetuximab (an EGFR inhibitor, 20 μ M). We demonstrated that blockade of EGFR signaling provides analgesia using an acute model of oral cancer pain in which mechanical allodynia is induced by injection of oral cancer cell line supernatant into the paw of a mouse. Intraperitoneal injection of Cetuximab (1mg) attenuated the nociceptive response compared with controls injected with saline (N=7 both groups, $P<0.05$). These observations implicate oral cancer secreted EGFR ligands in the activation of EGFR signaling in the peripheral nervous system to induce oral cancer pain.

Disclosures: E. Salvo: None. R. Veeramachaneni: None. K. Singh: None. D. Albertson: None. B. Schmidt: None. Y. Ye: None.

Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.08/EE11

Topic: D.03. Somatosensation: Pain

Support: KAKENHI (26462824)
Miyata Research Grant in A

Title: Noxious lingual stimulation influences the cortical excitability

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Abstract: Pain reduced motor function. And pain also reduced excitability of cortical motor region (e.g., primary motor cortex), but not subcortical region (e.g., pyramidal tract and motor nuclei). However, the mechanism of reduction of cortical motor activity by peripheral noxious stimulation is unclear. Recently, the voltage-sensitive dye imaging revealed that the peripheral (e.g., tongue) stimulation induced region specific excitatory responses in the middle region (approximately 1 mm rostral from middle cerebral artery) of the agranular subregion of insular cortex (AI). And the involvement of layers II/III pyramidal neurons in the middle region of AI with these responses was confirmed by *in vivo* whole-cell patch clamp recording. The amplitude of tongue stimuli-induced evoked excitatory postsynaptic potentials (eEPSPs) was dependent on both the stimulation intensity and the membrane potential oscillation of AI pyramidal neurons. Moreover, the involvement of GABAergic transmission in the membrane potential oscillation as well as the sensory processes from tongue is determined. In this study, we

investigated the effects of noxious lingual stimulation on the neural activity in several cortical regions (e.g., insular cortex and primary motor cortex (MI)). *In vivo* whole-cell patch clamp recording from middle region of AI and tongue region of MI was performed. To reconstruct morphological feature of recorded cells, only one neuron was recorded in each animal. Pyramidal neurons exhibited spontaneous membrane oscillation. Electrical stimulations (7 V) of around recording region elicited eEPSPs (11.5 ± 2.9 mV, $n = 8$). Repetitive electrical stimulation with 5 pulses at 50 Hz induced summation of eEPSP. Noxious lingual stimulation was applied by infusion of the algescic chemical glutamate (10min, 20 μ l, 120 μ l/h).

Disclosures: K. Adachi: None.

Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 057.09/EE12

Topic: D.03. Somatosensation: Pain

Support: NSFC Grant 81671100

Title: Immunohistochemical analysis of histone H3 acetylation in the TREZ on TN animal model

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Abstract: Object Trigeminal root entry zone (TREZ) is a transitional zone between the central nervous system (CNS) and peripheral nervous system (PNS) adjacent to the brainstem. TREZ compressed by microvascular was considered to be the primary aetiology in most cases of trigeminal neuralgia (TN), but whether epigenetic regulation involved in the pathogenesis of TN is still unclear. Thus, this study was designed to investigate the epigenetic regulation of histone H3 acetylation in TREZ in TN animal model. **Methods** To measure the length of the central portion of the TREZ from the junction of the trigeminal nerve root entering pons to the interface of the dome-shaped CNS-PNS transitional zone, immunofluorescent staining of glia and glial nuclei was performed with glial fibrillary acidic protein (GFAP) antibody and DAPI, respectively. To investigate the acetylation of histone H3 within the TREZ in TN animal model group and sham operation group, localization of Histone H3K9, H3K18 and H3K27 acetylation was examined by immunohistochemical staining methods. **Results** Measurements of the CNS-PNS transitional zone in the TREZ revealed that the average length from the conjunction of the trigeminal nerve root connecting pons to the glial fringe of the TREZ in the TN group was longer than that in the sham operation group ($p < 0.05$), and it gradually migrated distally. Cells that

stained positive for acetylated histone H3K9, H3K18 and H3K27 were distributed around both sides of the border of the CNS-PNS junction in the TREZ. The ratio of immunoreactive H3K9-, H3K18- and H3K27-positive cells in the TN group was obviously higher than that in the sham operation group on post operation day 7, 14, 21 and 28 ($p < 0.05$). **Conclusions** These results suggested that chronic compression of trigeminal nerve root may be involved in the pathogenesis of TN animal model by influencing the plasticity of CNS-PNS transitional zone and level of histones acetylation in the TREZ.

Disclosures: D. Luo: None.

Poster

057. Somatosensation: Trigeminal Processing

Location: SDCC Halls B-H

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Program #/Poster #: 057.10/EE13

Topic: D.03. Somatosensation: Pain

Support: NIH Grant EY028143

Title: Sex related microglia activation contributes to ocular hyperalgesia in a rat model for dry eye

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Abstract: Objectives. The mechanisms for persistent ocular hyperalgesia in dry eye disease (DE) are not known. This project determined if purinergic receptor P2x7 and microglia activation in the trigeminal brainstem nuclear complex (TBNC) plays a role in persistent ocular hyperalgesia in a rat model for tear deficient DE.

Methods. The left exorbital gland was excised 2 weeks prior to testing in adult male rats and ovariectomized female rats without (OvX) and with estradiol supplement (OvXE). Under urethane, long duration orbicularis oculi electromyographic activity (OOemgL), a measure of squinting, a nocifensive behavior, and ocular hyperalgesia was evoked by ocular application of hypertonic saline (HS). The influence of P2x7R on evoked OOemgL was assessed by injection of A804598 into TBNC of sham and DE rats. In separate rats, isolated microglia from TBNC were analyzed by qPCR for expression levels of P2X4, P2X7, and products of microglia activation (NLRP3 inflammasome, IL-1 β) in sham, DE and DE+A804598 groups. Densitometry (blinded analyses) was used to assess protein levels of Iba1, P2x7, GFAP, IL1 β and NLRP3 in TBNC tissue.

Results. HS-evoked OOemgL activity was enhanced in DE rats (OvXE = OvX >> male) and corresponded well with Iba1 staining for microglia in TBNC. Injection of A804598 into TBNC reduced HS-evoked OOemgL (OvXE = OvX > male). Isolated microglia from DE rats had

elevated expression levels of P2X4, P2X7, NLRP3, and IL-1 β (OvXE > OvX > male). Flow cytometry confirmed that infiltrating immunocytes did not contribute to these results. Densitometry revealed increased protein levels of Iba1, GFAP, P2x7 and NLRP3 in TBNC of OvX and OvXE rats, but not males. Systemic administration of A804598 (4 days) reduced the expression of P2x7, IL1 β and NLRP3 in TBNC of DE rats but not in sham controls, consistent with local drug-induced reduction of HS-evoked OOemgL.

Conclusions. These data demonstrate that microglia activation in the TBNC plays a significant role in ocular hyperalgesia in sex-dependent manner. These results further suggest that the P2x7 receptor may be a target for drug development to manage persistent ocular hyperalgesia in moderate to severe cases of DE.

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Poster

057. Somatosensation: Trigeminal Processing

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Program #/Poster #: 057.11/EE14

Topic: D.03. Somatosensation: Pain

Support: The work was supported by generous donations from TN patients and family members
NIH grant R01NS064988

Title: Functional GABAA receptors in the trigeminal but not sciatic nerve of the rat

Authors: *J. B. PINEDA FARIAS¹, J. E. LOEZA-ALCOCER¹, M. GOLD¹, R. SEKULA²
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Abstract: Despite clinical evidence that inclusion of a positive allosteric modulator of GABAA receptors to solutions used for regional anesthesia increases the duration post-operative pain relief, preclinical evidence suggests this is not due to a direct action of the positive allosteric modulator on the peripheral nerve. In contrast, however, the antiepileptic drug carbamazepine is effective in a subpopulation of patients suffering from classic trigeminal Neuralgia (TN), in particular those suffering from pain associated with vascular compression of a trigeminal nerve, while this drug has failed to demonstrate efficacy in clinical trials concerning other neuropathic pain conditions, even those associated with peripheral nerve compression injuries. Given that carbamazepine is both a GABAA receptor agonist and a blocker of voltage-gated Na⁺ channels (VGSC), and that few differences have been described between trigeminal and somatic nerves with respect to the VGSC present, we hypothesized that these clinical observations reflected a differential distribution of GABAA receptors in somatic and trigeminal nerves. To test this, we employed rat models of somatic (sciatic nerve, SN-CCI) and trigeminal (infraorbital nerve, ION-

CCI) nerve compression, and assessed the sensitivity of the compound action potential (CAP) in the SN and ION to Carbamazepine alone and in the presence of a GABAA receptor antagonist, picrotoxin or the GABAA receptor agonist, muscimol. We observed that the potency of carbamazepine-induced CAP block was greater in the ION than the SN, and this difference was potentiated by CCI of the ION. The potency of carbamazepine-induced block of the ION was reduced in the presence of picrotoxin. The potency of muscimol-induced block of the ION was greater than the SN, and CCI produced a further increase in efficacy. These results suggest functional GABAA receptors are present in the ION but not SN. This differential distribution of GABAA receptors could account for the therapeutic selectivity of carbamazepine for the treatment of TN.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.01/FF1

Topic: D.03. Somatosensation: Pain

Title: Oxytocin receptors on PACAP38 sphenopalatine ganglia neurons

Authors: N. A. MANERING¹, M. KLUKINOV², X. XIE⁴, *D. C. YEOMANS³

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Abstract: Background: Activation of parasympathetic sphenopalatine ganglia (SPG) neurons is implicated as a critical step in the pathogenesis of cluster and some migraine headaches. In particular, activation of these neurons appears to release PACAP-38 onto the dura matter, where it causes mast cell degranulation and subsequent vasodilation. When infused, PACAP-38 induces headache as well as facial flushing in patients. Thus, mechanisms by which inhibition of SPG neuronal activity and subsequent release of PACAP-38 is potentially of great clinical utility. We have previously demonstrated that oxytocin, acting at oxytocin receptors on trigeminal ganglia neurons inhibits those neurons, reduces the release of CGRP and inhibits craniofacial pain in rodents and migraine headache in patients. Thus, it is of interest to determine whether SPG neurons also possess oxytocin receptors and whether these receptors are co-localized with PACAP-38. Here we performed immunohistochemical experiments examining the expression of oxytocin receptors and PACP-38 on SPG neurons.

Methods: Rats were injected bilaterally with 50 μ L of CFA into the vibrissal pads to induce robust inflammation which has been shown to induce overexpression of oxytocin receptors. Two days later, rats were deeply anesthetized and transcardially perfused with fixative. Their SPG

was removed and cryoprotected overnight in 20% sucrose. Thereafter SPG was cryosectioned (10 μ M) and slices were processed for PaCAP-38 and oxytocin receptor immunofluorescence using specific antibodies. Sections were also stained with DAPI to show nuclei. Sections were then examined using epifluorescence microscopy for immunoreactivity to the two antigens. Z stacks were also created to determine intracellular localization.

Results: Examination of sections demonstrated clear expression of oxytocin receptors on most SPG neurons. In addition, as previously reported, many cell also showed expression of PACAP-38. Extracellular PACAP-38 was also observed. More than 50% of oxytocin receptor positive neurons were also positive for PACAP-38. Z-stack analysis demonstrated that while cellular PACAP-38 was primarily located cytoplasmically, oxytocin receptors were located along neuronal cell membranes as well as in the cytoplasm.

Conclusions: These results indicate oxytocin receptors are present on SPG neurons and that many of these neurons also contain PACAP-38. Given the demonstrated inhibitory effect of oxytocin on peripheral neuronal firing, it is possible that oxytocin might also inhibit the firing of SPG neurons, inhibit PACAP-38 release, and have a therapeutic effect on cluster headache.

Disclosures: **N.A. Manering:** None. **M. Klukinov:** None. **X. Xie:** 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.; Afasci, Inc.. **D.C. Yeomans:** None.

Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.02/FF2

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant Number18K06884

Title: Sensitization of trigeminal-parasympathetic circuit cause post traumatic headache

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Abstract: Mild traumatic brain injury (mTBI) accounts for the majority of head injuries, and posttraumatic headache (PTH) is the most common adverse effect. The most PTH has migraine-like phenotype (Hyperalgesia, Photophobia, Throbbing pain) and is difficult to resolve. It is well known that shock-wave induced traumatic brain injury. Recent studies show that laser-induced shock wave (LISW) lead to mTBI. The goal of this study is to establish a new model for PTH using LISW and to reveal the neural basis for PTH. The parietal region of male rats was irradiated with laser-induced shock wave (diameter 3mm, 4J/cm²) under barbiturate anesthesia.

In awake male rats, ocular surface application of hypertonic saline (2.5 M) evoked eye wipe behavior that was enhanced after mTBI. And also, in TBI rats, light-aversion behavior was enhanced compared to naïve rats. In separate rats, under isoflurane anesthesia, single cornea/dura responsive neurons were recorded at the trigeminal subnucleus caudalis (Vc). Hypertonic saline (2.5M) and blight light (irradiance=50, 300, 500 W/m²) selectively activated ocular surface and intraocular (neurovascular system), respectively. In TBI rats, Vc units had enhanced responses to hypertonic saline and blight light compared to naïve rats. To determine if mTBI caused bright light evoked intracranial blood flow increases, blood flow was monitored in arteries of the exposed cranial dura mater and the parietal cortex in naive and TBI rats. In TBI rats, bright light enhanced the magnitude of blood flow but not naive rats, and this blood flow increases evoked dura-responsive Vc units activities. Additionally, in TBI rats, bright light-increased dural blood flow was markedly inhibited by 10min after CoCl₂ injection into the subnucleus interpolaris/caudalis (Vi/Vc) transition, whereas blockade at the caudalis/upper cervical junction (Vc/C1) regions had no effect. It is concluded that mTBI produces a chronic state of hyperalgesia and light evoked vessels dilation that is reflected in the sensitization of trigeminal - parasympathetic circuit. This model may be suitable for future studies of migraine.

Disclosures: **A. Tashiro:** None. **H. Ohta:** None. **Y. Morimoto:** None.

Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.03/FF3

Topic: D.03. Somatosensation: Pain

Support: NIH-NIDA R01DA040688
NIH-NIDA 3R01DA040688-02S1
Department of Psychiatry at UIC
Graduate Program in Neuroscience at UIC

Title: Delta opioid receptor activation inhibits cephalic allodynia in multiple models of headache

Authors: ***L. S. MOYE**, A. F. TIPTON, K. M. SIEGERSMA, W. WITKOWSKI, N. SHAMSHUDDIN, A. A. A. PRADHAN
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Abstract: Headache disorders are highly disabling and are some of the most common disorders worldwide. Therapeutic options for headache are limited, and we recently identified the delta opioid receptor (DOR) as a promising therapeutic target for migraine. Here, we further characterize the effectiveness of DOR agonists in other headache models including: medication overuse headache by sumatriptan (MOH), opioid-induced hyperalgesia (OIH), and post-

traumatic headache (PTH). We also determined the effect of DOR activation on the expression of calcitonin gene related peptide (CGRP), an endogenous migraine generator, within a mouse model of chronic migraine. C57Bl/6J mice were used throughout these experiments. For MOH and OIH, mice were chronically treated with sumatriptan or morphine, respectively. PTH was modeled by combining the closed head weight drop model with the nitroglycerin (NTG) model of chronic migraine. Cephalic mechanical allodynia developed in all four models; and an acute injection of SNC80, a hallmark DOR agonist, significantly attenuated this allodynia in all cases. Furthermore, in an NTG model of chronic migraine, repeated SNC80 treatment inhibited acute migraine-associated pain, and additionally prevented the development of chronic cephalic hypersensitivity. Chronic treatment with NTG also resulted in an increase in CGRP expression within the trigeminal ganglia and trigeminal nucleus caudalis; and this increase was not observed when animals were co-treated with SNC80. Together, our results show that the DOR could be effective for multiple types of headache, and that it can regulate CGRP in headache related regions.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.04/FF4

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01NS099292

Title: Is NHE1 involved in migraine pathology and regulation of triptans uptake?

Authors: *E. LIKTOR-BUSA¹, K. COTTIER¹, E. GALLOWAY¹, T. W. VANDERAH, Ph.D.², T. M. LARGENT-MILNES³

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Abstract: The classical function of the blood–brain barrier (BBB) is the regulation of the transcellular and paracellular transport between the CNS and the vasculature. Nonetheless, recent studies have raised the possibility that changes in the BBB permeability might be associated with pain, including episodic headache. Disruption of the BBB by pain and cortical spreading depression (CSD) may alter analgesic efficacy or CNS toxicity of anti-migraine therapeutics, including first-line therapies like triptan compounds. The low efficacy level of triptans (only 30% of patients have reduced pain intensity and duration, and triptans should be taken before the headache phase of migraine) suggests an undiscovered pharmacokinetic mechanism of action of triptans that may relate to dysfunction of BBB integrity. The clarification of biochemical

mechanisms regulating migraine-induced changes in BBB function is crucial to understand the efficacy of antimigraine drugs. In order to investigate the BBB changes caused by migraine attack we established an in vivo model of episodic headache utilizing dural cannulation method and in vitro models of neurovascular unit. In our in vivo model of episodic headache, we demonstrated that cortical KCl injection induced CSD event, long-lasting periorbital allodynia and enhanced cortical uptake of ¹⁴C-sucrose and ³H-sumatriptan. Moreover cortical KCl injection decreased the expression level of NHE1 protein (45% ±14 of naïve), a proton exchanger, which may alter the uptake kinetics of sumatriptan and contribute the severity and duration of headache. In order to further investigate the role of NHE1 in migraine pathology and confirm our in vivo observations, we utilized immortalized (bEND3) and primary endothelial cells, as in vitro models of neurovascular unit. In our model, KCl treatment negatively influenced the transendothelial electrical resistance (TEER) (65.26% ±11.75 of baseline vs. 90.43 % ±13.5 % of baseline, KCl treated vs. saline treated group) and increased the fluorescein transport (130% of saline treated group), suggesting the disruption of endothelial function after KCl treatment. Our preliminary results suggest that total expression of NHE1 is temporally regulated after KCl treatment in vitro, moreover estradiol revealed regulatory effect on the expression level of NHE1. Using trans-well strategy, we quantified sumatriptan uptake of intact and NHE1 knock-out (CRISPR-Cas9 gene edited) endothelial cells before and after KCl treatment. This study thus promises to advance our understanding of BBB integrity during episodic migraine and determine how CNS uptake of antimigraine therapeutics is regulated during attacks.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.05/FF5

Topic: D.03. Somatosensation: Pain

Support: NIH-NIDA Grant DA040688

Title: HDAC inhibitors as novel therapeutic targets for migraine

Authors: *Z. J. BERTELS¹, A. TIPTON¹, L. S. MOYE¹, I. DRIPPS¹, P. SHAH¹, B. KARUMUDI², V. PETUKHOVA², P. A. PETUKHOV², G. R. J. THATCHER^{2,3}, A. A. PRADHAN¹

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Abstract: Migraine is a highly prevalent and debilitating disorder with limited therapeutic options. Many chronic conditions are accompanied by changes in neuroplasticity including alterations of histone deacetylases (HDAC), which in turn results in altered chromatin dynamics and gene expression. HDACs can be divided into four major families with the majority classified under Class I and II. The aim of this study was to investigate the role of HDAC inhibition in migraine. Chronic migraine-associated pain was induced by treating male and female C57BL6/J mice every other day for 9 days with the human migraine trigger, nitroglycerin (NTG; 10 mg/kg, IP). On test days, basal and post-injection mechanical responses were determined in cephalic or hind-paw regions. Twenty-four hours after the final NTG/VEH injection, animals were tested with vehicle, the pan-HDAC inhibitor trichostatin-A (TSA; 2 mg/kg IP), a novel brain-penetrant pan-HDAC inhibitor (RN-73; 10 mg/kg), or a novel Class I-selective HDAC inhibitor (ASV-85; 10 mg/kg); and subsequently tested for mechanical responses. Repeated NTG produced chronic long lasting cephalic and hind-paw allodynia. TSA and RN-73 effectively reversed this hypersensitivity within 2-4 hours of injection, and this effect was lost 24hr post-treatment. In comparison, the Class I selective inhibitor, ASV-85, was less effective and altered nociception in general. Our results suggest that histone deacetylase induction could be a mechanism maintaining the chronic migraine state; but that Class I HDACs alone are not sufficient for this regulation. This work also opens the possibility of developing HDAC inhibitors for the treatment of migraine.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.06/FF6

Topic: D.03. Somatosensation: Pain

Support: electroCore Task Agreement

Title: Vagus nerve stimulation attenuates trigeminal nociception similarly to sumatriptan in two rat models of episodic migraine

Authors: *L. CORNELISON¹, S. WOODMAN¹, J. L. HAWKINS², P. L. DURHAM³
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Abstract: *Objective:* The goal of our study was to compare a novel treatment for migraine to the clinical standard of sumatriptan in two models of episodic migraine.

Background: Neck muscle tenderness is a common risk factor reported in migraine patients,

while pungent odors are a reported trigger. We have previously reported that neck muscle inflammation lowers the activation threshold of trigeminal neurons to exposure of an extract of the “headache tree” that results in increased nociceptive responses in the V1 and V3 dermatomes. Additionally, we have evidence that transdermal, noninvasive vagal nerve stimulation (nVNS) is effective at aborting increased nociception after exposure to the odorant trigger by decreasing several proteins implicated in trigeminal sensitization. However, this model has not been validated by comparison with the existing nitric oxide migraine model and nVNS has not been compared to sumatriptan, a standard anti-migraine drug.

Methods: Sprague Dawley rats were used to observe nocifensive responses to von Frey filaments. To induce neck muscle inflammation, complete Freund’s adjuvant (CFA) was injected at 10 neck muscle sites. Eight days post CFA, trigeminal neurons were activated by exposure to volatile compounds from the extracted oil of the California bay leaf tree (CBL) for 10 minutes, or injection of sodium nitroprusside (SNP; 0.01 mg/kg, i.p.). Nocifensive head withdrawal response to mechanical stimulation was investigated 2 hours post exposure to the trigger. To ameliorate nociception, animals received vagus nerve stimulation or 0.3 mg/kg sumatriptan given subcutaneously. To stimulate the vagus nerve, electrodes were placed over the cutaneous area directly above the nerve and a 1 ms pulse of 5 kHz sine waves, repeated at 25 Hz for 2 minutes was administered to the animal 2 times, 5 minutes apart. Head withdrawal response was investigated 1 hour and 24 hours post treatment.

Results: Animals exposed to either SNP or the CBL oil that also had muscle inflammation exhibited increases in nocifensive responses in both the V1 and V3 regions. This increased nociceptive response was effectively reduced by administration of either nVNS or sumatriptan two hours post-trigger.

Conclusion: Our findings provide evidence that an odorant stimulus can act similarly to a known vasodilator as a trigger of orofacial pain in sensitized animals. In addition, nVNS can abort the increased nociception mediated by muscle inflammation in conjunction with either trigger, similarly to sumatriptan. Thus, we propose that nVNS may be useful as a nonpharmacological therapy for migraine and likely TMD, since both are co-morbid with neck muscle pathology.

Disclosures: **L. Cornelison:** 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.; electroCore. **S. Woodman:** 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.; electroCore. **J.L. Hawkins:** None. **P.L. Durham:** 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.; electroCore.

Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.07/FF7

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant Number JP17K15458

Title: Visualization of weather-related headache pathology by implantable CMOS imaging device

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Abstract: Migraine is a common neurovascular disorder characterized by severe headaches and is associated with dysfunction of the autonomic nervous system. Notably, some patients who have migraine seem to be more sensitive to changes in the weather such as atmospheric pressure and humidity. Although there are several useful prophylactic or therapeutic medicine, the pathophysiology of headache, especially in weather-related headache, is poorly understood. To investigate the mechanism of weather-related headache, we focused on the change in cerebral blood flow (CBF) occurring in the process of headache and measured CBF change by using the implantable CMOS imaging device for detecting hemodynamic signal in freely moving mice. Moreover, to reproduce the change of the weather, we made a climatic chamber that can change atmospheric pressure and humidity. In the present study, atmospheric pressure was lowered by 50 hPa, kept at this level for 10 and 30 minutes, and returned to the previous level. During the low atmospheric pressure period, implantable CMOS imaging device detected the CBF increase in both large vessels and microvessels. Although CBF gradually recovered to the basal level after return to the basal atmospheric pressure level, it fluctuated irregularly. Furthermore, low atmospheric pressure caused the change in aquaporin 4 (AQP4) expression in astrocytes in the brain. These results suggest that disturbance of CBF interacting with glial function contributes to the mechanism of weather-related headache.

Disclosures: **Y. Kurauchi:** A. Employment/Salary (full or part-time):; Kumamoto University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; JSPS. **M. Haruta:** None. **R. Tanaka:** None. **H. Kawamoto:** None. **T. Seki:** None. **K. Sasagawa:** None. **J. Ohta:** None. **H. Katsuki:** None.

Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.08/FF8

Topic: D.03. Somatosensation: Pain

Title: Pharmacological characterization of the rat inflammatory soup dural stimulation model of episodic and chronic migraine

Authors: *M. URBAN, K. ALVIRDE-VEGA, H. ZHAO, D. POSAVEC, L. HODGE, P. H. HUTSON, S. E. BROWNE
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Abstract: Infusion of inflammatory soup (IS) onto the dura of rats has previously been shown to produce both transient and persistent facial hypersensitivity, and these responses are believed to mimic episodic and chronic migraine, respectively. In the present study, several analgesic compounds were evaluated in the rat IS dural stimulation model to examine the pharmacology associated with transient and persistent facial hypersensitivity. Male Sprague Dawley rats were implanted with a screw guide cannula over the dura, and rats received either 1 or 5 infusions (1 per day) of IS (2 mM serotonin, histamine, bradykinin, 0.2 mM PGE₂, pH 5; 10 µl). Facial sensitivity was measured by applying calibrated von Frey filaments to the periorbital region of the face and determining facial sensitivity thresholds (i.e. facial swipe/head withdrawal). Study groups were randomized, the investigators were blinded to treatment, and the study groups were sufficiently powered (n=7-12/group). A single infusion of IS produced a transient (2 hour) facial hypersensitivity that was prevented by pretreatment with the NSAID naproxen (50 mg/kg), the mu opioid agonist morphine (5 mg/kg), the 5-HT_{1B/1D} agonist sumatriptan (1 mg/kg), the CGRP receptor antagonist olcegepant (1 mg/kg), the delta opioid agonist SNC80 (30 mg/kg), and the mGluR5 NAM dipraglurant (50 mg/kg). Following 5 infusions of IS, rats developed persistent facial hypersensitivity that was only partially inhibited by sumatriptan (2 mg/kg). The plasma exposures for sumatriptan in these studies were consistent with exposures required for clinical antimigraine efficacy (100 ng/ml). Additionally, sumatriptan was not detected in the brain, supporting a peripheral mechanism of action. These data demonstrate that pretreatment with a variety of clinically effective antimigraine therapies can prevent the development of transient facial hypersensitivity. That sumatriptan was only partially effective in inhibiting persistent facial hypersensitivity is consistent with clinical reports demonstrating reduced efficacy in chronic migraine. The similarities between pharmacology observed in the IS dural stimulation rat model and the clinical setting supports the use of this model for the development of novel antimigraine therapies.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.09/FF9

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01AT007176

Title: Effects of sleep quality, pain catastrophizing, anxiety and depression on pain-related activation for migraine patients and healthy controls

Authors: *J. ZHANG¹, A. KEARSON², S. BURROWES¹, L. SAMAWI^{1,2}, B. L.

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Abstract: Introduction Migraine is a debilitating pain disorder that affects millions of people with a high comorbidity in psychiatric disorders such as anxiety and depression. The goal of this study is to identify effects of sleep quality, pain catastrophizing, anxiety and depression on acute pain processing in migraineurs and healthy controls using fMRI. Method We enrolled 104 episodic migraine patients and 35 matched healthy controls who completed measures of sleep quality (Pittsburgh Sleep Quality Index), pain catastrophizing (Pain Catastrophizing Scale), depressive symptoms (Patient Health Questionnaire -9), and anxiety (Generalized Anxiety Disorder-7). Sensory testing determined heat pain threshold, which was used to select subject-specific painful temperatures (pain ratings of 5-6 out of 10) administered periodically during two fMRI scans. Participants rated the maximum and average pain intensity at the end of each scan and all analyses controlled for pain ratings. A GLM approach was defined for each participant, and one-sample t-test was used to test the relationship between psychological measures and acute pain processing. The initial voxelwise threshold was set at $p < 0.001$ with correction for multiple comparisons at the cluster level. Results Heat pain thresholds and temperatures used during the scan were similar between patients and controls, while patients had higher pain ratings compared to controls. Controls had a positive association between sleep scores and pain-related activity in the precuneus (PCu), postcentral gyrus, superior frontal gyrus and posterior insula. For pain catastrophizing, patients showed a negative relationship in PCu. For depression scores, patients showed a negative relationship for pain-related activity in the anterior insula and a positive relationship in precentral gyrus and bilateral putamen, while controls showed a positive relationship with and precentral gyrus, postcentral gyrus and PCu. For anxiety, patients showed a

positive relationship in left amygdala and left putamen. Conclusion Among controls, lower quality sleep and higher levels of depression were associated with greater pain-related activation in insula, PCu, and postcentral gyrus. However, migraineurs show a pathological pattern. The negative association between PCu and pain catastrophizing in migraineurs suggests increased attention toward pain, which is consistent with prior literature. In addition, migraine is associated with anxiety-related hyperactivity in the limbic system.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.10/FF10

Topic: D.03. Somatosensation: Pain

Support: NIH Grant DE017805

Title: Novel model for development of a persistent sensitized state of trigeminal nociceptors: Implications for understanding chronic migraine

Authors: *S. E. WOODMAN¹, J. L. HAWKINS², L. CORNELISON², H. G. CHILDS², P. L. DURHAM²

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Abstract: Objective: The goal of this study was to investigate the combined effects of REM sleep deprivation, prolonged inflammation of the trapezius muscle, and exposure to a pungent odor on nocifensive behaviors and expression of inflammatory proteins in the spinal trigeminal nucleus (STN).

Background: Chronic migraine is characterized by sensitization of trigeminal nociceptive neurons. Clinically, neck muscle tenderness and pain and sleep deprivation are considered risk factors for development of chronic migraine while pungent odors are commonly reported triggers of migraine. Stress can manifest as neck muscle tension and cause disruption of normal sleep cycles such that the time spent in REM sleep is reduced. While animal models that mimic aspects of episodic migraine pathology have been established, there is a need for models of chronic migraine characterized by persistent trigeminal sensitization and sustained nociception.

Methods: Sprague Dawley rats were injected with complete Freund's adjuvant in the trapezius to cause prolonged inflammation, and REM sleep deprived for one night to promote trigeminal sensitization. Following 7 days of recovery, trigeminal neurons were activated by exposure for 10 minutes to volatile compounds from the extracted oil of the California bay leaf tree (CBL). Nocifensive head withdrawal response to von Frey filaments applied to the cutaneous area over

the temporalis (V1) and masseter (V3) was measured for up to 63 days post CBL exposure. Immunohistochemistry was used to determine changes in the expression of CGRP, PKA, GFAP, and Iba1 on day 63 in the STN.

Results: Animals subjected to muscle inflammation, REM sleep deprivation, and CBL were unresponsive to mechanical stimuli 2 hours post CBL exposure but became responsive on day 1, then exhibited a sustained increase in the average number of nocifensive head withdrawals until day 49. The expression of CGRP, PKA, and GFAP, but not Iba1, were elevated in the medullary dorsal horn 63 days post odor exposure.

Conclusions: Our results demonstrate that neck muscle inflammation and REM sleep deprivation can promote development of a persistent sensitized trigeminal system that can be activated by exposure to a pungent odor, which is known to trigger migraines in humans. In addition, exposing sensitized animals to CBL resulted in a transient unresponsive state like that reported by migraine patients during a severe attack. Together, our findings provide evidence that we have developed a model of trigeminal sensitization and activation similar to chronic migraine, which can be used to study the molecular mechanisms involved in the transition from episodic to a more chronic nociceptive state.

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Poster

058. Somatosensation: Pain: Headache and Migraine

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 058.11/FF11

Topic: D.03. Somatosensation: Pain

Title: De novo protein synthesis is necessary for priming in preclinical models of migraine

Authors: *J. LACKOVIC, M. SURESH, T. PRICE, G. DUSSOR
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Abstract: Despite its prevalence as the third most common disorder worldwide, the underlying pathophysiology associated with migraine is still poorly understood. Migraines are often triggered by stimuli that are normally non-noxious. Similarly, in pre-clinical models of headache, mice and rats exhibit hypersensitivity to innocuous stimuli after recovery from an initial pain-inducing stimulus, a model referred to as priming. The primed state may be mediated by *de novo* protein synthesis using the cap-binding eIF4F complex, the convergent target of the Ras-ERK and PI3K-mTOR pathways. The purpose of these studies was to determine whether cap-dependent translation is necessary for priming in a preclinical model of migraine. To test whether general local protein synthesis contributes to priming, wild-type (WT) female ICR mice were given a supradural injection of the pro-inflammatory cytokine IL-6, in the absence or

presence of the protein synthesis inhibitor anisomycin. The animals were then tested for periorbital hypersensitivity using the von Frey method. Once animals returned to baseline, they were given a second supradural injection of a normally subthreshold stimulus of pH 7.0 to test for the presence of priming. The role of cap-dependent translation in priming was assessed by utilizing eIF4E knock-in (4EKI) mice. Priming was induced using a repeated restraint stress model since stress is the most commonly reported migraine trigger. Male and female 4EKI or C57/Bl6 WT mice were stressed for two hours a day for three days and then tested for facial hypersensitivity. Once animals returned to baseline following stress, they were given a sub-threshold dose of the nitric oxide donor sodium nitroprusside (SNP, 0.1 mg/kg) and again tested for mechanical hypersensitivity. Animals that were co-injected with IL-6 and anisomycin showed similar acute facial hypersensitivity compared to the IL-6 alone group; however, once the animals returned to baseline, only the IL-6 alone group responded to dural pH 7.0 with robust periorbital hypersensitivity. Likewise, there was no difference in acute facial hypersensitivity between stressed 4EKI and WT mice; however, after return to baseline, only WT animals exhibited significant periorbital hypersensitivity with sub-threshold SNP. Using two different models of priming to induce migraine-like behavior, these findings demonstrate that protein translation does not contribute to acute facial hypersensitivity with dural IL-6 or stress, but it is necessary for the development of priming. Our data suggest a role for *de novo* protein synthesis in events contributing to hypersensitivity to innocuous stimuli in migraine patients.

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Poster

058. Somatosensation: Pain: Headache and Migraine

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant R35HL140031
NIH Grant R01DA041809

Title: Specific PKC isoform mediates ongoing pain in a mouse model of migraine

Authors: *Y. HE, Z. J. WANG

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Abstract: Migraine is one of the most common neurological disorders characterized by recurrent attacks of typically throbbing and unilateral headache, affecting up to 20 % of the population worldwide. Despite the high prevalence and severity of this primary headache disorder, limited progress has been made in understanding and treating migraine. By characterizing and validating a mouse migraine model, this study aimed to investigate the functional contribution of PKC

isoforms in migraine. Systemic administration of NO donor, nitroglycerin (NTG) induced significant and prolonged mechanical hypersensitivity in female mice. We found the presence of migraine-like ongoing pain in mice after chronic intermittent treatment of NTG. The peptide antagonist of calcitonin gene related peptide (CGRP), α CGRP (8-37) effectively blocked ongoing pain and elicited pain relief-induced CPP in NTG-treated mice. Prominent activation of specific PKC isoform was observed in the superficial laminae of the spinal cord dorsal horn in chronic NTG-treated mice. Functional inhibition of the PKC isoform significantly attenuated ongoing spontaneous pain in chronic NTG-treated mice. Furthermore, we recapitulated the NTG-triggered migraine model in PKC isoform-null mice. In response to repeated administration of NTG, ongoing spontaneous pain was not developed in mice lacking the specific PKC isoform. This study is the first to identify the presence of ongoing pain in mice treated with nitroglycerin, a known human migraine trigger that closely resembles the common manifestation of spontaneous migraine attacks in humans. These findings demonstrated a critical regulatory role of spinal PKC in migraine pathophysiology, which may offer new pharmacological targets for anti-migraine treatment.

Disclosures: Y. He: None. Z.J. Wang: None.

Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 059.01/FF13

Topic: D.07. Vision

Support: ARC grant DP180100636
ARC grant DP170102263

Title: The development of the neural code in the zebrafish optic tectum

Authors: *L. AVITAN, Z. PUJIC, A. MYHRE, J. MÖLTER, N. C. LAMB, B. SUN, G. J. GOODHILL
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Abstract: Developing animals must transform sensory input into motor output adaptively as their neural representations mature. Several properties of the neural code, such as selectivity, variability and correlation structure, play an important role in the ability of the network to encode and decode sensory information. The larval zebrafish begins to hunt at 5 dpf (days post-fertilization) while the visual system is still maturing. However it is unknown how the neural code changes over early life, and what impact this has on the development and performance of hunting behaviour. To address this we recorded both spontaneous neural activity, and neural activity evoked by small spots appearing in different positions in the visual field, using 2-photon

calcium imaging of GCaMP6s larvae at different ages. Prior to imaging, hunting episodes were videoed for each fish. Preliminary results indicate changes in receptive fields, tectal correlation structure, and decoding performance. Together these findings suggest that tectal information processing refines over development.

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Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 059.02/FF14

Topic: D.07. Vision

Support: ERC-StG 311159

Title: An inter-hemispheric neural circuit in the zebrafish optic tectum required for efficient prey hunting

Authors: *F. DEL BENE¹, C. GEBHARDT¹, T. AUER¹, K. DUROURE¹, I. H. BIANCO²
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Abstract: Larval zebrafish show complex goal-directed hunting behavior that seems to be mainly guided by vision and requires sensory integration to detect the prey and a series of specific locomotor maneuvers to track it. During hunting, zebrafish larvae converge their eyes thereby considerably increasing the overlapping field of view. Furthermore, the final capture swim is being stereotypically initiated when the larva is at a distance of about 0.5mm to the prey. These evidences suggest that larva might be able to estimate object distance by using binocular visual information. However, given that the larva has entirely crossed projections from the eyes to the visual brain, the interpretation of binocular information on this connectional level, like e.g. found in mammals, is unlikely. Thus the neural substrate for such a mechanism in zebrafish is as of yet unknown. We recently identified a zebrafish line that expresses Gal4 in a previously undescribed commissural neuron population in the brain. We found these neurons to be bilaterally-symmetrically distributed adjacent to the ventral tectum. Furthermore, they connect the tectal halves, form synapses there and were thus termed intertectal neurons (ITNs). We reasoned that ITNs might be good candidates for the potential transfer and/or the integration of binocular visual signals and that they thus might have a role during larval prey capture.

We next unilaterally ablated ITNs with 2p imaging and subsequently examined free-swimming behaviour of ablated vs. ctrl fish during an assay of prey capture. Ablated fish hunted less efficiently than wild-type but basic motor parameters were not affected. However, ablated fish showed a drastically diminished probability of initiating capture swims when close to the prey,

arguing that ITNs might indeed play a role in the last step of the prey hunting sequence, the initiation of the capture swim. Using 2p Ca imaging, we established that ITNs respond to moving bars and small dots simulating moving prey. Furthermore, after unilateral eye-ablation, we observed Ca transients in the tectal hemisphere not receiving any retinal input that were co-localized with the trajectories of the contralateral ITN arbors suggesting that ITNs might transfer prey-specific information to the ipsilateral tectum with respect to the prey. In summary, we anatomically describe novel, previously unknown, inter-hemispheric neural connections in the zebrafish visual system, establish their role in inter-tectal visual signal transfer and show that they are important for the successful completion of the hunting behavior sequence.

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Poster

059. Subcortical Visual Pathways

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Parkinsonfonden

Title: Mechanisms for saliency coding and transmission from the lamprey tectum to the SNc/VTA

Authors: ***J. PÉREZ-FERNANDEZ**, B. ROBERTSON, S. GRILLNER
Karolinska Inst., Stockholm, Sweden

Abstract: The dopaminergic system was already well developed at the dawn of vertebrate evolution, according to data in lampreys. The SNc/VTA modulation of the basal ganglia through the direct and indirect pathways in the striatum is already present in these animals, and its connectivity is virtually identical to that of mammals. This includes SNc/VTA direct projections to different motor centers, and the same neurons that project to the striatum also send collaterals to the optic tectum (superior colliculus), which controls orienting/evasive movements. The SNc/VTA direct modulation of tectum has profound effects on its motor commands, acting on two subpopulations of tectal neurons expressing either D1 or D2 receptors, which are able to enhance or suppress neuronal activity respectively. Dopaminergic modulation of the striatum and

tectum is therefore performed in parallel. Direct projections from the SNc/VTA allow a fast modulation of tectum to better react to salient stimuli (meaning here the ability to stand over other stimuli), which evoke a dopaminergic activation. Here, we investigate the mechanisms coding saliency in the SNc/VTA. Using a preparation maintaining the eyes together with the brain, we applied visual stimuli to analyze the impact in the SNc/VTA of different aspects involved in saliency (including speed, intensity and size), showing that activity in the SNc/VTA increases in parallel with the saliency of the applied stimulus. Given that visual information to the SNc/VTA comes from tectum, we explored how this last region codes and transmits saliency to the SNc/VTA. Our results show that tectum alone is sufficient to transmit saliency information to the SNc/VTA. The increase in activity parallel to saliency persists in the SNc/VTA after inactivation of other brain regions influencing tectum and/or SNc/VTA, including the parabigeminal nucleus, pallium (cortex), or the habenula. However, responses to visual stimuli are abolished in the SNc/VTA when locally injecting kynurenic acid in tectum, confirming that saliency coding arises in this last region. Saliency information is transmitted to the SNc/VTA from a group of tectal neurons that form a defined population in the anterior part of the visual map, rather than being spread throughout tectum. Performing patch-clamp recordings of these neurons, we have also analyzed the synaptic mechanisms for saliency coding in tectum. Our results show that the tectal inhibitory interneurons have a key role in how saliency is transmitted to the SNc/VTA. Given the high degree of conservation of the dopaminergic system and the optic tectum, this study provides the evolutionary bases for saliency detection in the SNc/VTA.

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Poster

059. Subcortical Visual Pathways

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Title: Motion-sensitive neurons in the nucleus of the basal optic root in hummingbirds (*Calypte anna*) and zebra finches (*Taeniopygia guttata*)

Authors: ***A. H. GAEDE**^{1,2}, **G. C. SMYTH**¹, **D. R. WYLIE**², **D. L. ALTSHULER**¹

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Abstract: As birds move through their environment, large-field visual motion, or global optic flow, is processed by two retinal recipient nuclei, the nucleus of the basal optic root (nBOR) and the nucleus lentiformis mesencephali (LM). The nBOR, part of the accessory optic system, and the LM of the pretectum are involved in retinal stabilization and optic flow analysis. Furthermore, the LM is hypertrophied in hummingbirds, and to a lesser extent in transiently hovering birds, suggesting a neural specialization for hovering (Iwaniuk and Wylie, 2007). LM cells also have different response properties in hummingbirds compared to zebra finches and pigeons (Gaede et al., 2017). Specifically, whereas in zebra finches and pigeons (and all tetrapods) the majority of neurons prefer temporal-to-nasal motion, in hummingbirds the distribution of direction preferences is uniform. Moreover, with respect to stimulus speed, hummingbird LM neurons preferred much faster speeds. Because the LM and nBOR share reciprocal projections and play a role in visual guidance, we recorded from the nBOR of hummingbirds and zebra finches to determine whether species differences in response properties exist in this region as well. As in the LM, neurons in the nBOR show increased firing in response to motion in their preferred direction, and suppression of spontaneous firing in response to motion in the opposite direction. In the present study, using standard electrophysiological techniques and computer-generated stimuli (a single plane of random dots), we characterized the response properties of nBOR neurons, and found that the visual motion direction preferences are similar in hummingbirds and zebra finches. These data are consistent with previously published results in pigeons (Morgan and Frost, 1981; Gioanni et al., 1984; Wylie and Frost, 1990). Cells in the nBOR prefer motion in either up, down, or backward directions, and are inhibited by motion in their anti-preferred direction. There is a topographical representation of direction preference in the nBOR. The ‘up’ cells are located in the dorsal region of nBOR, ‘down’ cells are located ventral to ‘up’ cells, and ‘back’ cells are located ventro-laterally. In addition to being direction-tuned, nBOR neurons are tuned to stimulus velocity. Most of these cells, in both hummingbirds and zebra finches, preferred slower velocities than LM cells. In a previous LM study, we found very few neurons tuned to slow velocities in hummingbirds. In summary, although the response properties of LM neurons are different in hummingbirds compared to other birds, those of nBOR neurons are similar across species.

Disclosures: A.H. Gaede: None. G.C. Smyth: None. D.R. Wylie: None. D.L. Altshuler: None.

Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

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Program #/Poster #: 059.05/FF17

Topic: F.01. Neuroethology

Title: *In vitro* tracing reveals intranuclear connectivity in the pigeon’s nucleus subpretectalis/interstitio-pretecto-subpretectalis

Authors: *M. J. ACERBO¹, O. GUNTURKUN²

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Abstract: Earlier, we have proposed that the nucleus rotundus (Rt) and the nucleus subpretectalis/interstitio-pretecto-subpretectalis (SP/IPS) may provide a plausible substrate that could perform figure-ground segregation in the avian brain (Acerbo & Lazareva, 2018). Our proposed circuitry incorporated an earlier hypothesis that suggested a presence of collateral projection to the Rt and the SP/IPS from the optic tectum (Tombol, Nemeth, Sebesteny & Aplar, 1999; Theiss, Hellmann & Gunturkun, 2003). In addition, our proposed circuitry suggested that the neurons in the SP/IPS share GABAergic inhibitory connections that are stronger for the neurons responding to the similar features. This study was the first step toward confirming the existence of such intranuclear connectivity in the SP/IPS by using in vitro biocytin crystals injections. We used a vibratome to obtain thick coronal slices (800 µm) of pigeon's brain, and injected biocytin crystals into the SP/IPS area. Slices were then incubated in artificial cerebrospinal fluid for 4-6h. After that, they were fixed in 4% paraformaldehyde solution, cryoprotected, and re-sectioned into 30 µm slices using a freezing microtome. The slices were further processed for immunohistochemistry using a DAB reaction, and Nissl stained. The resulting images of the SP/IPS areas showed extensive intranuclear SP/IPS projections. Because 90% of the SP/IPS projections are inhibitory, we conclude that the SP/IPS contains an extensive intranuclear inhibitory network that has been proposed in our earlier work.

Disclosures: M.J. Acerbo: None. O. Gunturkun: None.

Poster

059. Subcortical Visual Pathways

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Program #/Poster #: 059.06/GG1

Topic: H.01. Animal Cognition and Behavior

Support: Fondecyt 1170027

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Title: A matrix thalamo-pallial pathway in birds

Authors: M. FERNÁNDEZ, M. VERGARA, E. SENTIS, *G. J. MARÍN, J. MPODOZIS

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Abstract: The existence of ascending projections from the dorsal thalamus to the pallial telencephalon is one of the most distinctive characteristic of the amniote brain. In mammals, these efferents have been classified in two major types: i) first order (core) projections, originated mainly from the sensory nuclei and directed towards the internal layers (mainly layer

4) of specific sensory cortices; and ii) higher order (matrix) projections, originated by a matrix of cells surrounding the sensory nuclei, and directed towards more external, associative cortical layers (mainly layers 1-3). At present, matrix projections are believed to be exclusive of mammals. In birds, thalamic ascending fibers end onto discrete areas in two distinct pallial territories: the hyperpallium and the dorsal ventricular ridge (DVR). Recent studies regarding the anatomical organization of the sensory areas of the DVR have shown that these areas share a common neuroarchitectural motif, featuring three radially interconnected, and functionally differentiated layers: an internal one, receiving “core” afferents from specific dorso-thalamic sensory nuclei; an intermediate one, which serves an associative role connecting to other pallial areas; and a more external one, which mostly participate in the recurrent interlaminar circuitry. In the present study we reassessed the organization of the thalamic projections to the visual DVR, performing “in vivo” neural tracing studies in adult pigeons. In addition to the well-known first order projection from the thalamic nucleus rotundus (Rt) to the internal layer of the visual DVR (Entopallium), we found a “higher order-like” projection, originated by cells surrounding the Rt and adjacent thalamic nuclei, and ending specifically into the intermediate layer of the visual DVR (Intermediate Nidopallium, NI). Moreover, these thalamic neurons seem to form a continuous extranuclear matrix of cells projecting, besides the NI, to several associative areas in the lateral pallium, and to the arcopallium (avian equivalent to the motor cortex). In addition, we found that these thalamic neurons receive weak sensory projections as well as descending projections from the arcopallium and the hyperpallium. These observations led us to propose that this extranuclear thalamo-pallial system of projections could be the avian equivalent to the higher order, or matrix, system of thalamocortical projections of mammals. Furthermore, these observations support our previous proposition that the NI is the avian counterpart to the superficial layers of the mammalian cortex.

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Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 059.07/GG2

Topic: D.07. Vision

Support: University of Strasbourg
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Title: The 3-step map alignment algorithm models visuotopic defects in the midbrain of Isl2-EphA3KI mutants

Authors: *M. REBER^{1,2}, E. SAVIER^{2,3}, A. BATHELEMY², F. W. PFRIEGER²

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Abstract: Understanding and modelling the mechanisms of neural maps formation in the brain has been a challenging subject in neurobiology for several decades. One of the most studied structure, from experimental and theoretical standpoints correspond to the superior colliculus (SC), a major hub involved in visual attention and orientation, receiving organized inputs from visual, auditive and somatosensory modalities. Visual inputs in the superficial layers of the SC correspond to organized projections from the retinal ganglion cells (RGCs) in the eye (the retino-collicular map) and to organized projections from layer V neurons in the primary visual cortex V1 (the cortico-collicular map). Both visual topographic maps must be aligned and in register in the SC. The retino-collicular system attracted a lot of the computational work because the knowledge of the molecular mechanisms controlling map formation is far more advanced compared to any other neural mapping system. In particular, the mapping mechanisms of the nasal-temporal axis of the retina onto the rostral-caudal axis of the SC, involving EphA receptors and EfnA ligands, have been, by far, the most studied and modelled. Many different algorithms have been generated and were further optimized as soon as new experimental data were available. The recent 3-step Map Alignment algorithm simulates the development of the retino-collicular map and the subsequent alignment of the cortico-collicular projections along the rostral-caudal axis of the SC. This model contains experimentally measured and estimated levels of EphAs/EfnAs graded expression in RGCs, SC and V1 cortex. The basic mechanism, demonstrated previously (Savier et al., 2017), consists of the transposition of the retinal EfnA gradients into the SC during retino-collicular mapping. These transposed retinal EfnA gradients subsequently provide positional information for incoming cortico-collicular projections, controlling the alignment of the visual maps. Here, using the 3-step Map Alignment model combined to in vivo map analyses, we demonstrate that this algorithm not only simulates normal maps alignment in WT but also models the fully and the partially duplicated retino/cortico-collicular maps in respectively the Isl2-EphA3KI homozygous and heterozygous mutants. Savier et al., 2017. A Molecular Mechanism for the Topographic Alignment of Convergent Neural Maps. *eLife* 6:e20470.

Disclosures: M. Reber: None. E. Savier: None. A. Bathelemy: None. F.W. Pfrieger: None.

Poster

059. Subcortical Visual Pathways

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Program #/Poster #: 059.08/GG3

Topic: D.07. Vision

Support: NIH T32

Title: Do retinal ganglion cell axons project to multiple targets?

Authors: *K. HENG^{1,2}, S. H. SHAH³, J. L. GOLDBERG^{1,2}

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Abstract: Retinal ganglion cells (RGCs) send visual information to the brain through the optic pathway. Tracing studies have demonstrated that individual RGCs belonging to various subtypes arborize and target multiple areas in the brain. However, the branching patterns of RGCs have not been fully characterized, and the significance of conserving the branching pattern during regeneration after injury is unclear. To identify RGCs that project to multiple areas of the brain, RGCs were labeled by stereotactic injection of retrograde AAV delivering multiple distinct fluorophores to multiple RGC target areas. Multi-target projection was inferred and categorized when an RGC exhibited co-labeling of multiple fluorophores. This study provides a foundation for further genetic manipulation, such as neuronal activity inhibition with retrograde AAV, of RGCs with multi-target projections to determine the functional significance of RGCs that synapse to multiple targets.

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Poster

059. Subcortical Visual Pathways

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Title: Behavioral modulation of retinal boutons in mouse superior colliculus

Authors: *S. SCHRÖDER¹, N. A. STEINMETZ¹, M. KRUMIN¹, M. RIZZI¹, L. LAGNADO², K. D. HARRIS¹, M. CARANDINI¹

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Abstract: Visual responses in multiple brain regions, including visual thalamus and primary visual cortex (V1), are modulated by non-visual factors such as locomotion and arousal. We observed that this modulation extends to the superficial layers of superior colliculus (sSC), which receive direct visual input from the retina, and asked where this modulation may originate. To record the activity of neuronal populations within sSC, we used two-photon calcium imaging while mice were head-fixed and free to run on a treadmill. We presented drifting gratings of varying directions or a uniform gray screen to measure spontaneous activity. To track arousal level, we measured running speed and pupil diameter.

About 50% of neurons in sSC were significantly correlated with running and pupil diameter both during spontaneous and visually driven activity. Roughly equal numbers of neurons showed positive and negative correlations. Changes in arousal also had significant effects on direction tuning curves. These effects could be described with a linear model (additive shifts plus multiplicative effects) but were heterogeneous across neurons.

To investigate whether these behavioral effects were inherited from V1, we inactivated V1 by optogenetically stimulating inhibitory neurons, while recording from ipsilateral sSC neurons using Neuropixels probes. V1 inactivation decreased average visual responses in sSC, but did not significantly decrease modulation by locomotion and arousal.

We then tested whether behavioral modulation originates in the retinal input to sSC. We imaged calcium activity in boutons of retinal ganglion cells (RGCs) located in sSC. To our surprise, locomotion and arousal correlated with bouton activity and modulated the boutons' direction tuning. Correlation with locomotion even persisted in darkness, excluding the possibility that these effects could be explained by pupil dilation changing the light levels that reach retina. This observation might be explained by (1) modulation of RGC output by behavior, e.g. via backprojections from the rest of the brain, or (2) modulation of retinal boutons in the sSC, e.g. via neuromodulators causing changes in calcium levels. To test the first hypothesis, we recorded from the optic tract and preliminary results indicate that retinal firing rates are modulated by running and arousal.

Taken together, our results show that neuronal responses in the superficial layers of SC are not solely driven by visual inputs but are also modulated by locomotion and arousal. This modulation is not inherited from V1, but rather originates as early in the visual pathway as in the retinal input to sSC.

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Poster

059. Subcortical Visual Pathways

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Pew Scholar Award (A.D.H.)

Title: Genetic and functional dissection of retinotectal pathways for modulation of pupil size

Authors: *O. S. DHANDE¹, T. A. SEABROOK², A. H. PHAN², N. ISHIKO², P. L. NGUYEN², J. T. WANG², A. D. HUBERMAN^{2,3}

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Abstract: The olivary pretectal nucleus (OPN) is a principal station in the neural pathway for generating the pupillary light reflex (PLR), an evolutionarily-conserved central reflex. Inputs from functionally-distinct retinal ganglion cell (RGC) types are organized within specific domains of the OPN namely, the peripheral OPN ‘shell’ and central OPN ‘core’. Although the compartmentalized architecture of the OPN has been recognized for decades, the functional relevance of those compartments to the PLR has remained elusive. We identified the T-box family transcription factor Tbx20 as a molecular marker of a unique optic pathway that preferentially encodes dorsal visual space. A major target of these Tbx20 expressing retinal ganglion cells (Tbx20-RGCs) is the OPN core. We discovered that genetically removing Tbx20 function in OPN projecting RGCs results in a severe reduction in Tbx20-RGC axonal inputs to the OPN core. Surprisingly, the loss of Tbx20-RGCs alone did not lead to a severe deficit in the PLR. However, when we abolished melanopsin-photopigment mediated signaling as well as Tbx20-RGCs we observed a dramatic disruption in the PLR suggesting a hierarchical functional organization of parallel pathways within the OPN. To more directly assess the contribution of OPN-core projecting RGCs we used a novel intersectional genetic strategy to chemogenetically activate this pathway in a highly selective manner. We used the Cre-DOG (dependent on GFP) system to retrofit OPN-core projecting RGCs to express hm3D, an excitatory designer receptor exclusively activated by designer drugs. Chemogenetic activation of OPN-core projecting RGCs resulted in a marked dilation of the pupil. Our data suggests a putative “push-pull” system for controlling pupil aperture. The OPN-shell drives pupil constriction (push) (Güler et al., 2008) whereas the OPN-core projecting RGCs drive pupil dilation (pull) and thereby dynamically control the full range of PLR behavior. These data therefore represent a step towards dissecting the specific function of different types of RGCs and in doing so, provide new insight into the distinct functional roles of the different OPN anatomical compartments and pathways.

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Poster

059. Subcortical Visual Pathways

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Program #/Poster #: 059.11/GG6

Topic: D.07. Vision

Title: Signatures of complexity in feed-forward pathways of the visual thalamus

Authors: *A. R. CASTI

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Abstract: The spiking of visual neurons in the lateral geniculate nucleus (LGN) is influenced by a complex set of inputs that include feed-forward retinal excitation, feed-forward inhibition from local interneurons, and feedback collaterals from the reticular nucleus and primary visual cortex. There is also diversity within each category of inputs depending on the specifics of the circuitry in which a particular LGN cell is embedded. For example, the arrival times of feed-forward inhibitory inputs to a specific LGN cell can either be locked at a fixed delay relative to retinal ganglion cell inputs, or temporally uncorrelated to these same retinal inputs (Blitz and Regehr, 2005). The anatomical differences underlying these distinct types of feed-forward suppression can produce LGN spike trains with different timing signatures relative to an external stimulus as well as retinal input. The goal of this work is to explore whether a diagnostic measure of complexity can detect these underlying anatomical differences in LGN spike trains recorded extracellularly. For this purpose, we use model integrate-and-fire neurons and focus on different models of feed-forward inhibition.

Among the most common measures of neural response include the spike rate (spikes/sec) and the Shannon Information rate (bits/sec). For both of these diagnostics it is relatively simple to design model LGN neurons embedded within significantly different circuits that produce identical spike and information rates. The field of complexity theory offers more promising, less degenerate measures, of which there are many (e.g. Kolmogorov complexity) depending on the application. A particular complexity measure advanced with spike trains in mind by Haslinger & Shalizi (2010), called the *computational complexity*, fits an optimal Hidden Markov Model (Causal State Model) to a spike train. This optimal model produces a formal measure of the spike train's complexity as well as a minimal set of "causal states," associated with refractory periods, pre-burst states, and so on, that depend on specific spike train features and, indirectly, on the underlying anatomy. Using spike trains from model neurons with different forms of feed-forward inhibition, we find that this measure of complexity, along with the states that the optimal Causal State Model generates, can reliably distinguish LGN neurons with feed-forward inhibition that is either locked or unlocked to retinal input arrival times. This gives further evidence that computational complexity is a useful supplement to standard measures typically used to quantify neural responses in early stages of vision.

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Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 059.12/GG7

Topic: D.07. Vision

Title: Correspondence of transcriptomically- and morphologically-defined cell types in the human, non-human primate, and mouse dorsal lateral geniculate nucleus

Authors: ***G. J. MURPHY**¹, T. BAKKEN¹, V. MENON⁷, S. A. SORENSEN¹, B. R. LEE¹, C. LEE², R. D. HODGE¹, O. PENN¹, Z. YAO¹, R. DALLEY¹, L. T. GRAYBUCK³, T. NGUYEN¹, E. J. GARREN¹, N. DEE¹, K. SMITH¹, G. D. HORWITZ⁸, E. LEIN⁴, H. ZENG⁵, B. TASIC⁶
²Modeling Analysis and Theory, ³Mol. Genet., ⁴Human Cell Types, ⁵Structured Sci., ⁶Cell and Circuit Genet., ¹Allen Inst. for Brain Sci., Seattle, WA; ⁷HHMI Janelia Res. Campus, Ashburn, VA; ⁸Physiol. and Biophysics, Univ. of Washington, Seattle, WA

Abstract: Abundant anatomical and physiological evidence supports the presence of at least 3 distinct types of principal/relay neuron in the dorsal lateral geniculate nucleus (dLGN) - i.e., the thalamic brain area that conveys visual information from the mammalian retina to the primary visual cortex. To identify differentially expressed genes for these cell types we performed single-cell or single-nucleus RNA-sequencing. In both human and macaque, supervised clustering of single-cell transcriptomes based on the area of dissection identified several genes (e.g. ROBO2, GPC5, CDH8, FOXP2) that are differentially expressed between excitatory neurons in the magno- and parvocellular layers. Unsupervised clustering of the same data, however, failed to partition magno- and parvocellular relay neurons into discrete clusters. Similarly, principal neurons in the dLGN of mature mice were difficult to segregate into distinct clusters on the basis of their transcriptomic profiles alone but, like their counterparts in higher mammals, could be categorized into at least 3 distinct groups on the basis of their dendritic processes. Together, these data suggest that (1) transcriptomic differences between canonical principal cell types in the mature mammalian dLGN are subtle relative to transcriptomic differences between principal cells of the mammalian visual cortex and (2) there is not necessarily a 1:1 correspondence between cell types defined by 'morpho-electric' and transcriptomic criteria.

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Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

Support: NIH Grant EY009593

Title: Visual properties of local interneurons in the murine visual thalamus

Authors: *A. GORIN¹, S. AHN², U. M. CIFTCIOGLU¹, F. T. SOMMER³, J. A. HIRSCH¹
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Abstract: Local inhibitory interneurons within the lateral geniculate nucleus (LGN) of the thalamus influence every spike that relay cells send to cortex. Visual processing in the LGN has been studied most intensively in cat, where almost all relay cells have receptive fields composed of two concentrically-arranged On and Off subregions. We previously showed that there are push-pull responses within each subregion—e.g., a bright light shone in an On subregion excites whereas a dark stimulus presented within that same subregion inhibits. Further, we found that local interneurons also have receptive fields with a center-surround structure in cat. Thus, we hypothesized that the push is supplied directly by retinal ganglion cells of the same center-sign as the target cell and the pull is conveyed disynaptically, via opposite-sign ganglion cells that innervate local interneurons. It was difficult, however, to target interneurons in cat *in vivo* because they are sparsely distributed, have small somas, and cannot be identified by extracellular metrics like spike statistics. Thus, with the dual goals of learning more about inhibition in thalamus and how this compares across species, we turned to mouse for the genetic tools it offers. Our initial studies of mouse LGN focused on relay cells. Using whole-cell recording *in vivo*, we found that the largest single class of relay cells had receptive fields with a center-surround structure and push-pull responses. The remaining murine relay cells have various types of On-Off receptive fields. We suspected that the circuits that generate push-pull might differ between species, as follows. In cat, dendrites of interneurons arborize within discrete regions of retinotopic space; by contrast, murine interneurons have dendrites that traverse large retinotopic distances, and thus likely have receptive fields too wide to explain localized inhibition. Thus, for rodent relay cells, we propose a scheme in which the pull derives from On-Off (or convergent input from On and Off) interneurons with large receptive fields. For example, a bright stimulus confined to the On-center of a relay cell's receptive field and falling within the receptive fields of the presynaptic interneurons would simultaneously evoke both excitation and inhibition in the relay cell, with excitation outweighing inhibition. A dark stimulus would elicit only inhibition, however, thus producing a response that resembles push-pull. We identified murine interneurons

via optogenetics and we that found their receptive fields were large. In a broader context, our results suggest that different types of circuits serve common functions across species.

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Poster

059. Subcortical Visual Pathways

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Support: NIH Grant EY024173
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Title: Role of the parabigeminal nucleus in the selection of visually evoked defensive behaviors in mice

Authors: ***J. B. WHITLEY**, B. BORGHUIS, K. L. WHYLAND, M. E. BICKFORD
Anatom. Sci. and Neurobio., Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: Recent studies have shown that innate defensive behaviors in mice, such as escape and freeze, can be reliably evoked via overhead presentation of a rapidly expanding black disc (loom stimulus) or a small, slowly moving black disc (sweep stimulus), respectively (De Franceschi et al. *Curr. Biol.* 2016). Pathways from the superior colliculus (SC) to the parabigeminal nucleus (PBG) or pulvinar nucleus (PUL) have been implicated in initiating these defensive responses (Wei et al. *Nat Commun.* 2015; Shang et al *Science* 2015, *Nat Commun.* 2018), but it is unclear how these pathways contribute to the selection of appropriate defensive behaviors following the presentation of different visual stimuli. To begin to examine this, we designed a testing chamber and custom Matlab program to present either sweeping or looming stimuli, and track the position of mice before and after stimulus presentation. We first tested 6 C57BL/6J mice with the loom stimulus, and found a significant increase (escape response) in average speed (pre-stimulus: 9.65 cm/s, stimulus: 13.81 cm/s, $p=0.001$). In contrast, 6 C57BL/6J mice tested with the sweep stimulus showed a significant decrease (freeze response) in average speed (pre-stimulus: 9.83 cm/s, stimulus: 5.63 cm/s, $p=0.0003$). Next, we injected a cre-dependent AAV DREADD (designer receptor exclusively activated by designer drug), which induces the expression of a modified human M3 muscarinic receptor (hM3Dq) and the fluorescent marker mCherry, into the PBG of mice that expresses cre recombinase in cells with choline acetyl transferase (ChAT-cre). Ten days after injection, the mice were tested for responses to sweeping stimuli. Thirty minutes prior to the presentation of the first stimulus, the mice were given intraperitoneal injections of sterile saline or the specific DREADD ligand,

Compound 21 (0.5 mg/kg), which activates the receptor to induce burst firing. In 3 mice with unilateral PBG expression of hM3Dq, in saline trials there was a significant decrease (freeze) in average speed (pre-stimulus: 7.57 cm/s, stimulus: 3.42 cm/s, $p=0.024$), whereas in compound 21 trials there was a significant increase (escape) in average speed (pre-stimulus: 6.60 cm/s, stimulus: 11.22 cm/s, $p=0.031$). These results suggest that unilateral activation of the PBG can switch the selection of visually-evoked behavioral responses. SC cells that project to the PUL respond to sweeping or looming stimuli (Gale and Murphy J Neurosci. 2016), and we have found that the PBG directly innervates SC cells that project to the PUL. Thus, the PBG may modulate SC output to the PUL to bias the selection of visually-evoked defensive behavior.

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Poster

059. Subcortical Visual Pathways

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Title: Superior colliculus and parabigeminal nucleus synaptic connections in the mouse

Authors: *K. L. WHYLAND, A. SLUSARCZYK, N. ZHOU, G. SOKHADZE, G. GOVINDAIHA, M. E. BICKFORD
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Abstract: Recently, projections from the superior colliculus (SC) to either the pulvinar nucleus (PUL) or the parabigeminal nucleus (PBG) have been shown to be involved in the initiation of visually-evoked defensive behaviors (such as escape or freezing). To elucidate the circuits underlying these behaviors, we characterized the synaptic connections that link the PBG, SC, and PUL. To examine SC to PBG projections, biotinylated dextran amine (BDA) was injected in the SC, and BDA-labeled SC terminals in the PBG ($n = 100$) were examined using electron microscopy in tissue stained with a GABA antibody. Of the BDA-labeled SC terminals in PBG, 19% were found to be GABAergic, while the remaining BDA-labeled terminals, and all PBG postsynaptic dendrites, were non-GABAergic. The existence of distinct GABAergic and non-GABAergic SC cell types that project to the PBG was confirmed by injecting a retrograde Cre-dependent virus in the PBG of GAD2-Cre or parvalbumin-Cre transgenic mice; in each mouse line, SC to PBG projection cells were labeled in the ipsilateral stratum griseum superficiale (SGS). Immunocytochemical staining revealed that SC-PBG cells labeled in parvalbumin-Cre

mice do not contain GABA (98.5%, $n = 66$), while SC-PBG cells labeled in GAD2-Cre mice do not contain parvalbumin (100%, $n = 104$). To characterize the synaptic properties of the projections of the PBG to the SC, a Cre-dependent virus was used to induce the expression of the fluorescent marker, tdTomato, and the channelrhodopsin variant, ChIEF, in the PBG of ChAT-Cre mice. These injections labeled a dense field of terminals in the ipsilateral and contralateral SGS. In slices of the SC maintained in vitro, optogenetic activation of PBG-SC terminals using high frequency blue light pulses induced excitatory postsynaptic responses in SGS neurons. The identity of SGS neurons that receive PBG input was revealed using transynaptic virus injections in the PBG to induce Cre-recombinase expression in postsynaptic cells. When combined with Cre-dependent virus injections in the SC of GAD67-GFP mice (a reporter line that labels GABAergic SC interneurons), or combined with retrograde Cre-dependent virus injections in the PUL, we were able to determine that PBG projections contact both SC interneurons ($n = 41$) and PUL-projecting wide-field vertical cells ($n = 202$). These results reveal the complexity of SC-PBG connections, which may increase or decrease activity levels in the PBG or PUL to initiate escape or freezing behavior in a context-dependent manner.

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Poster

059. Subcortical Visual Pathways

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Title: GABAergic synaptic connections within the visual sector of the mouse thalamic reticular nucleus: Extrinsic projections from the pretectum

Authors: ***T. GORDON, III**, J. B. WHITLEY, P. W. CAMPBELL, K. WHYLAND, S. P. MASTERSON, N. ZHOU, M. E. BICKFORD
Anatom. Sci. and Neurobio., Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: The thalamic reticular nucleus (TRN) is composed of GABAergic neurons that surround and innervate the dorsal thalamus. The TRN is divided into modality-specific sectors, identified by segregated connections with visual, auditory and somatosensory thalamic nuclei, and associated cortical areas. This organization suggests that the TRN can gate thalamic sensory transmission in a modality-specific manner. Recent studies of the mouse TRN indicate that

intrinsic GABAergic connections between TRN neurons are sparse, but that the TRN is innervated by extrinsic GABAergic sources (Hou et al. J Neurosci 2016). Using electron microscopy, we examined mouse TRN tissue stained with an antibody against GABA (tagged to gold particles) and found that TRN neurons are richly innervated by GABAergic synaptic terminals. To identify the sources of these terminals, we injected a cre-dependent herpes simplex virus (transported in the retrograde direction) in the TRN of GAD2-cre mice. These injections labeled cells primarily in the hypothalamus and pretectum (PT). We then injected a cre-dependent adeno-associated virus in the PT or hypothalamus of GAD2-cre mice. These injections labeled terminals in distinct sectors of the TRN; hypothalamus injections labeled terminals primarily in the rostral TRN (see also Herrera et al Nat Neurosci 2016), while PT injections labeled terminals specifically in the caudal/dorsal visual sector (vTRN). To examine the synaptic connections formed by the PT-vTRN terminals, biotinylated dextran amine (BDA) was injected in the PT, and TRN sections containing BDA-labeled terminals were prepared for electron microscopy and stained with a GABA antibody (tagged to gold particles). This analysis confirmed that PT-vTRN terminals contain GABA and synapse on GABAergic TRN dendrites. Finally, virus injections were placed in the PT of GAD2-cre mice to induce the expression of a fluorescent marker and channelrhodopsin. Slices of the TRN were prepared and maintained *in vitro* and whole cell recordings were obtained from vTRN neurons surrounded by labeled PT terminals. Optogenetic activation of PT terminals with blue light pulses initiated robust inhibitory postsynaptic current/potentials in vTRN neurons. These results indicate the modality-specific sectors of the TRN are inhibited by distinct extrinsic sources, and suggest that the vTRN may be inhibited in relation to eye or head movements required to attend to visual targets. The resulting disinhibition of the thalamic target of the vTRN (the dorsal lateral geniculate nucleus) could increase the transmission of visual signals once visual targets are acquired.

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Poster

059. Subcortical Visual Pathways

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Program #/Poster #: 059.17/GG12

Topic: D.07. Vision

Support: NIH Grant EY09593

Title: Spatial and temporal processing of visual signals in the mouse thalamic reticular nucleus

Authors: *U. M. CIFTCIOGLU¹, F. T. SOMMER², J. A. HIRSCH¹

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Abstract: Sensory information from the retina travels through the lateral geniculate nucleus (LGN) of the thalamus before reaching cortex. Within the LGN, ascending information is processed by two inhibitory circuits: feedforward input from local interneurons and feedback connections from the thalamic reticular nucleus (TRN). TRN has been associated with diverse functions such as processing sensory features (Vaingankar et al., 2012) and spatial attention (McAlonan et al., 2008; Halassa & Kastner, 2017). In past studies of cat, we explored the structure of receptive fields (RFs) in visual TRN and found that these represent specific features, consistent with a role in form vision. This work was done using methods of spike-triggered averaging adapted for the firing patterns of reticular cells; much like LGN relay cells, TRN cells fire either tonic (single) spikes or bursts, depending on the prior membrane voltage. We also quantified the sizes of the RFs, reasoning that if TRN plays a role in spatial attention, these should be spatially localized. Because RFs in TRN have diverse shapes, they cannot be measured using standard methods. Thus, we estimated the size of reticular RFs by calculating the significance of each pixel in the spike-triggered average (Soto-Sanchez et al., 2017). Consistent with the idea that TRN plays a role in spatial attention, we found that RFs in TRN and LGN were comparable in size at a given eccentricity, except in the far periphery where reticular RFs were larger. Studies of TRN in higher animals are technically challenging, however. Recently, mouse has become an important model for studies of attention (Wimmer et al., 2015). Thus, we asked how our findings in cat might compare to mouse. We recorded responses of optogenetically identified reticular cells to sparse and dense noise stimuli in VGAT-ChR2-EYFP mice. Like cat, there was significant overlap in the range of RF sizes in LGN and TRN. RF sizes in both structures ranged from small ($5\text{-}10^\circ$) to large ($25\text{-}30^\circ$), with a few fields in TRN reaching $\sim 50^\circ$. Also, murine reticular cells encoded complex visual features and for On-Off cells, one luminance contrast (bright or dark) was preferred, as in cat. We next compared the RFs computed from tonic or burst spikes for both species. The general shapes of the RFs were similar, even as the temporal dynamics and amplitudes of response differed. Compared with tonic spikes, bursts were preceded by a longer and/or stronger stimulus of non-preferred luminance contrast, consistent with the idea that burst and tonic spikes code different aspects of the visual environment (Sherman, 2001). Overall, our work suggests the role of TRN is highly conserved across species.

Disclosures: U.M. Ciftcioglu: None. F.T. Sommer: None. J.A. Hirsch: None.

Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

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Program #/Poster #: 059.18/GG13

Topic: H.01. Animal Cognition and Behavior

Support: Hampden-Sydney College Faculty Research Grant

Title: Response selection is impaired by unilateral lesions in the rostral thalamic reticular nucleus

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Abstract: The Thalamic Reticular Nucleus (TRN) monitors bidirectional transmissions between the dorsal thalamus and cortex and filters the output of the thalamus by way of GABAergic synapses. In the case of sensory systems, the TRN is given a role in selecting thalamocortical signals related to specific stimuli, the process of selective attention. The rostral TRN exerts a similar inhibitory modulation of thalamocortical transmissions originating in motor thalamic nuclei. This suggests an analogous role for the rostral TRN in the selection of situationally appropriate responses. For this study, unilateral lesions in the rostral TRN are hypothesized to remove inhibitory control of responses made contralateral to the lesion leading to a decreased ability to make cued responses ipsilateral to the lesion. Eight Long-Evans male rats (250-350g) were trained to make an observing response in the center of 3 holes. Then a light presented either directly above or below the rat's head cued nosepokes into the left or right hole. Correct responses were reinforced by water; incorrect responses were punished by a 3 sec timeout. After reaching criterion performance, unilateral injections of ibotenic acid produced lesions in the rostral TRN, some of which extended into portions of the ventral anterior nucleus of the thalamus and/or the internal capsule. The proportion of correct responses directed ipsilateral to the lesion declined during a 9-day period after testing resumed. There was a concomitant increase in the number of incorrect responses made in the hole contralateral to the lesion. The proportion of trials when a response was not made following either cue and the number of intertrial nose pokes into either side hole did not change. Reaction times to the cues and times to execute response to either side also were unchanged. Thus, the impairments in making responses ipsilateral to the lesion occur only when they are cued and are not due to the inability to respond to the cue. The data suggest that while the rat is making an observing response, it is primed to respond in either direction. When the cue for a response ipsilateral to the lesion follows, however, the diminished inhibition of the motor nuclei on that side weakens the ability to deselect the incorrect contralateral response. We propose that the sensory and motor sectors of the TRN are functionally similar.

Disclosures: G. Weese: None.

Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 059.19/GG14

Topic: D.07. Vision

Support: NIH Grant EY009593
NIH Grant EY024173
NIH Grant GM103436

Title: Ultrastructural comparison of synaptic connectivity of local interneurons in the carnivore and rodent visual thalamus

Authors: *S. AHN¹, A. KUMAR¹, J. B. WHITLEY², J. A. HIRSCH¹, M. E. BICKFORD²
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Abstract: Local interneurons in the lateral geniculate nucleus (LGN) of the thalamus modulate visual information that is relayed from the retina to the cortex; they provide feedforward inhibition to each other and to relay cells. There are substantial differences in the morphology of interneurons in carnivores or primates versus rodents. In cat and monkey, for example, interneurons have complex dendrites with rich branching patterns that are spatially restricted within the LGN, while in mouse and rat, interneurons have fewer dendrites and these arborize broadly across the LGN. This suggests that there are commensurate differences in interneuron connectivity across species. To explore this topic, we analyzed the synaptic inputs and outputs of GABAergic neurons in the ferret and mouse LGN at the ultrastructural level. GABAergic neurons were stained with an antibody against GABA tagged with gold particles so that it was possible to distinguish inhibitory from excitatory components of the tissue by the density of overlying gold particles. We used conventional criteria (see Bickford, ESN 2018 for review) to classify synaptic terminal types. We divided excitatory synapses made onto interneurons into three groups, those likely to originate from retina, cortex or thalamic relay cells, and divided GABAergic synapses onto interneurons into two groups, those that originate from dendrites versus axons. Our results show that there is a difference in the balance of excitatory and inhibitory input onto interneurons between species. That is, ferret interneurons received the majority of their input from retinal terminals and GABAergic terminals in a 1:1 ratio, whereas mouse interneurons received those inputs in a 3:1 ratio. Moreover, the ratio of total excitatory input to inhibitory input was 2:1 for ferret interneurons, whereas it was approaching 4:1 for mouse interneurons. Our results thus suggest that the inhibition interneurons supply to relay cells is more precisely regulated in ferret than in mouse.

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Poster

059. Subcortical Visual Pathways

Location: SDCC Halls B-H

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Program #/Poster #: 059.20/GG15

Topic: H.01. Animal Cognition and Behavior

Support: CNPq (Brazil) Ciência Sem Fronteiras PVE (F.Clasca)

Title: The marmoset monkey medial pulvinar thalamic nucleus innervates multiple higher-order cortical areas

Authors: *F. CLASCA¹, A. CÓRDOBA-CLAROS¹, R. R. R. M. DE LIMA², P. RUBIO-GARRIDO¹, P. A. G. MORAIS², E. S. DE NASCIMENTO, Jr.², J. S. CAVALCANTI²

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Abstract: The medial division of the pulvinar complex (MPul) is a region of the thalamus massively expanded in higher primates, and particularly in humans. Fragmentary data from studies in different non-human primate species indicate that MPul is connected to frontal, parietal, cingulate, insular and temporal areas. However, the organization of such diverse and divergent connections has never been investigated in a systematic manner. Here, we mapped the area and lamina distributions of the axons arising from small clusters of MPul neurons using both microiontophoretic injections of biotinylated dextran (BDA) in the thalamus or retrograde tracer deposits in the cortex. We also analyzed axon trajectories in the cerebral white matter and axonal varicosity number and size in the cortex. MPul was delineated from neighboring nuclei using, Nissl, acetylcholinesterase histochemistry and Vesicular Glutamate transporter 2 (VGluT2) immunolabeling. The VGluT2 labeling indicates that MPul virtually lacks subcortical glutamatergic inputs. MPul axons reach only high-level association and paralimbic areas. These are innervated from largely segregated cell clusters, each innervating the ventral or orbital frontal cortex, or the posterior parietal cortex, or the cingulate cortex, or the temporal and parahippocampal cortices. Some cells simultaneously innervate two or more of these distant cortical regions. In most areas, axonal varicosities (putative synaptic sites) are concentrated in layers 3b and 4 and layer 1. Additional, MPul axonal branches innervate the lateral amygdaloid nucleus and the matrix compartment of the putamen. These observations are consistent with the notion that PulM may act as a high-centrality hub selectively linking distant higher-order cortical areas. As such MPul cells may control functional connectivity in the fronto-parieto-temporal networks that allow complex cognition and multisensory-guided social behaviors.

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Poster

059. Subcortical Visual Pathways

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Program #/Poster #: 059.21/GG16

Topic: D.07. Vision

Support: Supported by the NIH Intramural Program

Title: Comparing cortical and thalamic face-selective neural responses in the macaque

Authors: *A. P. MURPHY¹, C. DENG², K. W. KOYANO³, B. E. RUSS⁴, D. B. MCMAHON⁵, D. A. LEOPOLD⁶

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Abstract: Clusters of neurons responding more strongly to images of faces than non-face objects are found throughout the primate temporal cortex and are thought to constitute a network for face processing. Face selective responses have also been observed elsewhere in the brain, such as in the superior colliculus, and pulvinar complex of the thalamus. However, it is unknown how these responses derive from, or contribute to, the better studied cortical responses. To address this question, we compared several response properties of isolated single units among cortical and pulvinar face-selective neurons. We recorded from three cortical face patches using chronically implanted microwire bundles, and recorded systematically across the pulvinar complex using linear electrode arrays. For all neurons recorded in eight monkeys, we evaluated the responses to the same set of briefly flashed images as well as a five-minute naturalistic visual movie. Within the pulvinar, we found that many face selective neurons were loosely clustered in the caudal portion of the inferior pulvinar, with a few also present in dorsal regions of medial and lateral pulvinar. Pulvinar neurons exhibited a broader range of response latencies for both the initial visual response as well as the face-selective component, compared to cortical face-selective responses, with some cells responding earlier than the earliest IT cells. Similarly, the temporal dynamics of visual responses in the pulvinar were more varied than those of IT cells. Approximately 20% of visually responsive pulvinar neurons showed strong and prolonged inhibition following the initial excitatory visual response - a response profile that was not observed in any of the cortical cells. For static images, the trial-to-trial response variability of face-selective neurons was comparable between thalamic and cortical cells; however, for dynamic videos and free viewing, responses in the pulvinar were much more variable than those in cortical face patches. Together, the results support the notion that face-selective pulvinar neurons are fed by diverse cortical and possibly subcortical face-selective neurons, and integrate selective visual responses with sensorimotor information.

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Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

Support: European Community Grant H2020-720270 (Human Brain Project SGA1)
European Community Grant FP7-604102 (Human Brain Project)

Title: A reexamination of the functional role of cortico-thalamic feedback in the early visual system through mechanistic modeling

Authors: D. GUARINO¹, J. ANTOLÍK², Y. FRÉGNAC¹, *A. P. DAVISON¹

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Abstract: A striking feature of the mammalian early visual system is that, at both the thalamic and cortical levels, the feedforward extrinsic connections are vastly outnumbered by the feedback and intrinsic reverberating connections. Extensive exploration has been devoted to the feedforward retino-thalamo-cortical pathway and modelling generally assumes a sequential operating architecture, contrasting with the anatomical loops described inside the thalamus or between cortex and thalamus. Some experiments have attempted to manipulate the corticofugal pathway, but the scarcity of test experimental conditions, the lack of reproducibility of functional observations, and the paucity of anatomical data currently limit our understanding of its putative functional role. To reach a more coherent account of the feedback loops, we built a large-scale spiking model of the cat early visual system, which was constrained by connectivity statistics determined in anatomical studies, single cell electrophysiological properties in vitro and in vivo, and functional measures of the evoked firing statistics in the intact and lesioned experimental conditions. Parametric determination of key variables of the model was iterated through the reproduction of experimentally recorded responses to six "reference" stimulus configurations. For each stimulus, the model was tested using a constructionist approach. We started from a feedforward open-loop model - having only retinal ganglion cells connected to lateral geniculate nucleus (LGN) relay cells. Then we incorporated a first feedback loop intrinsic to the thalamic level - made by LGN and peri-geniculate nucleus (PGN) cells. Finally followed by the full closed loop configuration of the intact early visual system - including the loop from cortex to thalamus. The resulting model provides both phenomenological and mechanistic explanations for specific functional features (receptive field opponency, surround suppression, orientation preference) and offers testable predictions for further exploration of the role of thalamo-cortical loop in low-level perception.

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Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

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Wenzhou Medical University, Project of State Key Laboratory of Ophthalmology, Optometry and Visual Science

Title: Human subcortical pathways for imminent collision detection with and without attention

Authors: *J. ZOU¹, S. HE², P. ZHANG¹

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Abstract: Detecting imminent collision information is essential for survival, but little is known about the underlying neural mechanisms in the human brain. Using high resolution fMRI, the current study investigated where and how looming stimuli were processed in the human brain. An incoming visual object was either on or off a colliding course with the observers' head. When observers attended to and judged the trajectory of the incoming stimuli, several subcortical regions including the superficial layers of the superior colliculus (SC), parabrachial nucleus (PBGN) and central medial amygdala, responded stronger to the stimulus on the collision than the near-miss trajectory. However, this sensitivity to collision was observed only for stimuli coming from the upper but not the lower visual field. Behavioral measures confirmed that observers were indeed more sensitive to collision information from the upper visual field. When observers' attention was diverted away from the looming stimuli, the collision sensitive activation from regions described above was greatly reduced. However, a different subcortical pathway consisting of the intermediate layer of SC and the ventral tegmental areas (VTA) was activated to detect collision information without attention. An upper visual field advantage was also observed in the unattended condition. These results suggest that different human subcortical pathways, SC_{superficial}- PBGN - amygdala and SC_{intermediate}- VTA, are responsible for detecting imminent collision with and without attention, respectively. Similar subcortical regions have been found in rodent studies responding to looming stimuli, suggesting that these collision detection pathways might be evolutionarily conservative.

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Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

Support: National Nature Science Foundation of China Grant 31322025
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Title: Robust detection of laminar activities in the human LGN with UHF fMRI

Authors: *P. ZHANG¹, Y. QIAN²

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Abstract: The lateral geniculate nucleus (LGN) is the thalamic station in the retinocortical projection and plays important roles in perception and cognition. Primate LGNs consist of six main layers of neurons with distinct functions and cell types. The ability to resolve layer-specific activities of the human LGN non-invasively has important neuroscience and clinical implications. Here we tested whether ultrahigh field fMRI at 7T could distinguish ocular as well as magno- and parvocellular layer-specific activities of the human LGN. Full contrast checkerboard stimulus was presented to the left and right eyes in alternation to selectively activate the eye layers of the LGN. Transient and sustained visual stimuli were carefully designed to selectively activate the M and P cells. BOLD signals in the LGNs were acquired with T2* (GE-EPI) and T2 (b-ssfp) weighted MRI pulse sequences at 1.0 or 1.2 mm isotropic resolution. Results showed a highly reliable eye-dominance pattern for each LGN of four subjects, which is a sandwiched organization of three layered sections, arranged in the medial-ventral to dorsal-lateral direction. The BOLD contrast between the M and P biased stimuli clearly revealed the M and P layers of each LGN, with the M section located more medial and ventral in relative to the P section. These laminar patterns were highly consistent between odd and even runs within each scanning session, as well as across sessions from different days. To further confirm this finding, we ran a simulation test based on Nissl stained images of the human LGN at 20 μ m resolution, with the BOLD point-spread function taken into account. The simulation results showed an identical pattern as found with fMRI. We conclude that BOLD fMRI at 7T is capable to resolve laminar activities in the human LGN, which could be valuable for future applications to investigate its function in human visual perception and cognition.

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Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

Support: ERC-Consolidator Grant SENSOCOM 647051

Title: A probabilistic atlas of the human lateral geniculate nucleus using ultra-high resolution 7T structural magnetic resonance imaging

Authors: *C. MÜLLER-AXT¹, L. KAUFFMANN^{1,2}, P.-L. BAZIN^{3,4}, K. VON KRIEGSTEIN^{1,5}

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Abstract: The lateral geniculate nucleus (LGN) is a key subcortical brain structure of the human visual system. Traditionally, non-invasive spatial mapping of the LGN proved challenging due to its small size and deep position within the brain. However, recent advances in magnetic resonance imaging (MRI) methodology have made it possible to map such subcortical nuclei at an unprecedented level of anatomical detail (van der Zwaag et al., 2016). We here provide an in-vivo probabilistic atlas of the human LGN using ultra-high resolution 7 Tesla structural MRI data. The MRI dataset consisted of 0.5 mm isotropic quantitative T₁ maps of N=27 healthy young adults (12 males, 15 females) with a mean age of 26.5 ± 3.8 years, as provided in the Open Science CBS Neuroimaging Repository (Tardif et al., 2016). The probabilistic atlas was created by means of manual segmentations of the LGN by two independent raters in FSLView (<https://fsl.fmrib.ox.ac.uk/fsl>). Segmentations of both raters were merged for each subject such that only those voxels that were segmented by both raters comprised the final LGN masks used for atlas generation. The segmentation procedure resulted in an average volume of 113.5 ± 13.3 mm³ for the left LGN and 120.9 ± 14.0 mm³ for the right LGN, which is in good agreement with previous in-vivo and post-mortem LGN volume estimates (Müller-Axt et al., 2017; Andrews et al., 1997). Inter-rater agreement of the manual LGN segmentations was high: mean Dice coefficient = 0.88 ± 0.02 (Dice, 1945); mean modified Hausdorff distance = 0.08 ± 0.01 mm (Dubuisson and Jain, 1994). To generate the LGN atlas, all MR images and LGN masks were normalized to a study-specific quantitative T₁ template, which was created using symmetric normalization diffeomorphic image registration (SyN) in ANTS (Avants et al., 2007). Following registration, LGN masks were averaged and SyN was used to warp the resulting probabilistic

atlas into MNI standard space. For validation purposes, we created a validation atlas based on a n=20 randomly selected subset of the data. The validation atlas was employed to predict LGN voxels for the remaining subjects (n=7) by comparing predicted LGN volumes with the merged manual segmentations. The voxel-wise comparison of the LGN masks yielded high prediction accuracy: mean Dice coefficients = 0.82 ± 0.03 and 0.83 ± 0.03 in the left and right hemisphere, respectively. Given the high prediction accuracy on individual subject level, we expect that the provided high-resolution in-vivo LGN atlas will be of great value for the neuroimaging community in facilitating reproducible and standardized future studies on the LGN and the human visual system.

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Poster

059. Subcortical Visual Pathways

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Program #/Poster #: 059.26/HH4

Topic: D.07. Vision

Support: NIH grant R01 EY026916
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Tab Williams Family Foundation

Title: Rehabilitation of hemianopia using the principles of multisensory integration

Authors: A. S. DAKOS, H. JIANG, B. E. STEIN, *B. A. ROWLAND
Neurobio. & Anat., Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Extensive damage to visual cortex via stroke or traumatic brain injury produces blindness in the contralesional hemifield. Using a cat model of this hemianopic condition, we have previously shown that this deficit can be ameliorated by a non-invasive training procedure (Jiang et al., 2015). Spatiotemporally concordant auditory and visual stimuli are repeatedly presented in the blind hemifield and, after only several weeks, vision is restored. So too are visual responses of ipsilesional superior colliculus (SC) neurons. Repeated exposure to individual modality-specific stimuli does not have a restorative effect. Presumably, recovery is induced by repeated episodes in which auditory inputs and visual inputs from undamaged regions converge on multisensory SC neurons, eliciting enhanced responses and increasing the sensitivity of SC neurons to these visual inputs. To test the predictions of this hypothesis, hemianopic cats were given exposure to auditory-visual stimulus configurations that do not elicit multisensory enhancement. Two such cross-modal paradigms were used: one in which the cues were spatially disparate, and one in which they were temporally disparate. Neither training

program ameliorated the deficit despite extensive training/testing. All animals were then provided cross-modal training with spatiotemporally concordant auditory-visual stimuli, which typically elicit enhance responses. Rehabilitation was rapidly induced in each animal, thereby confirming the previous findings and supporting the hypothesis that multisensory enhancement is a key feature in reestablishing visual responsiveness in ipsilesional SC neurons so that they can once again support contralesional visual behaviors.

Disclosures: **A.S. Dakos:** None. **H. Jiang:** None. **B.E. Stein:** None. **B.A. Rowland:** None.

Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

Support: NIH Grant EY026916.

Title: Ameliorating hemianopia by cross-modal training

Authors: ***H. JIANG**, B. A. ROWLAND, B. E. STEIN
Neurobio. & Anat., Wake Forest Sch. Med., Winston Salem, NC

Abstract: Previously we had shown that hemianopia, induced by large lesions of visual cortex, and causing degeneration of the ipsilesional lateral geniculate nucleus, can be reversed in a cat model by a non-invasive cross-modal sensory training paradigm. In this paradigm, hemianopic animals trained in a localization task were tested daily with spatiotemporally concordant pairs of visual-auditory cues presented within the blinded hemifield over several weeks. After approximately 4 weeks, this training restored the ability of these animals to respond to visual stimuli in the contralesional field, as well as rudimentary visual pattern discrimination capabilities. This rehabilitation was mirrored physiologically by the return of visual responsiveness in deep ipsilesional superior colliculus (SC) neurons. Subsequently we demonstrated that cross-modal exposure was effective in rehabilitating hemianopia even if it was provided only once a week for several hours while the animal was under ketamine anesthesia. The present experiments demonstrate that the effectiveness of this exposure is even greater than previously thought, and can be induced with far fewer exposure events. Earlier training paradigms exposed animals to 2400 cross-modal stimulus pairs over a 4 hour period in each training session. Here we show that the number of exposures can be reduced to only 600 per training session over a 1 hour period without significantly impacting the rate or efficacy of the recovery. However, lowering the exposure count to 100 per session over 10 minutes significantly slowed (halved) the recovery rate, although it did not change its ultimate efficacy or pattern. In all cases behavioral responses to visual stimuli returned first in central visual space and then

expanded to more peripheral locations, and were accompanied by the restoration of visual activity in deep (i.e., multisensory) layer SC neurons. These observations suggest that comparatively few cross-modal experiences are required to initiate changes in the functional circuitry underlying these capabilities, and these take several weeks to reach the point at which vision can be supported. Taken together, the results reveal that the neural changes by which hemianopia can be reversed are initiated very rapidly by comparatively few cross-modal experiences, and do not require active involvement in a task, or any of the reinforcement contingencies normally associated with learning, or any overt effort, or even an alert brain. These observations have direct implications for rehabilitative strategies for use with human patients.

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Poster

059. Subcortical Visual Pathways

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Topic: D.07. Vision

Support: NIH Grant EY026916
Tab Williams Family Foundation

Title: Sensory cues can avoid the multisensory transform

Authors: *N. BEAN, B. E. STEIN, B. A. ROWLAND
Wake Forest Sch. of Med., Winston Salem, NC

Abstract: The brain typically integrates cross-modal cues derived from the same event (e.g., are coincident in space and time). This process of multisensory integration amplifies their salience by enhancing the physiological responses of individual superior colliculus (SC) neurons and the overt detection and orientation behaviors they support. Previously it was demonstrated that the magnitude of this behavioral enhancement was roughly equivalent whether animals were trained to approach both cues (“redundant targets”) or only one cue (the second cue was either novel, or trained to elicit a “no-go” response). These observations suggest that animals make the best use of environmental information (i.e., the Bayesian prediction), which compels them to integrate cross-modal cues that are mutually informative. The present results show that this need not happen and reveal that the brain can functionally “hide” one of the inputs from the multisensory transform. Cats (n=3) were trained in a localization task with two pairs of V and A cues. The first pair (V1, A1) always appeared in concordance (never individually) and animals were rewarded for approaching them. The second pair (V2, A2) never appeared together, and animals were given a low reward for approaching one (V2), but no reward for the other (A2). The effects of all cues were then tested individually and in all possible combinations. Whereas V1A1 and V2A1

elicited robust and equal enhancements in accuracy, when the unrewarded auditory stimulus (V1A2, V2A2) was present, even in concordant cross-modal configurations, there was no enhancement. Responses were no more accurate than to the visual cue alone. This striking difference was reversed when animals were re-trained with the stimulus identities reversed. It is important to note that even a novel auditory cue (A3) elicited robust enhancement when paired with either visual cue. In short, redundant targets, novel stimuli, and stimuli trained with conflicting responses (no-go vs. approach) all generate very robust and very similar multisensory enhancements. But animals can be trained to not integrate a particular cue with any others, rendering it unavailable to the multisensory transform. This is surprising not only because the normal effects of cross-modal inputs can be voided by learning, but also because the underlying circuit can avoid using information that would be informative in the context of the task - a finding in conflict with some basic theoretical assumptions of multisensory integration.

Disclosures: N. Bean: None. B.E. Stein: None. B.A. Rowland: None.

Poster

060. Visual Categorization and Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 060.01/HH7

Topic: D.07. Vision

Support: NIH R01EY019466
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2016R1C1B2015901

Title: Reward may evoke visual perceptual learning following reinforcement learning rules

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Abstract: Visual Perpetual learning (VPL) is defined as long-term performance improvement as a result of visual experiences (Watanabe & Sasaki, 2014). VPL occurs when such experience involves active engagement of a task relevant to the features being trained. Alternatively, VPL also occurs when the trained features are exposed irrelevantly to the main task being performed. The former refers to task-relevant VPL and the latter to task-irrelevant VPL. Several studies have demonstrated that reward evokes task-irrelevant VPL. However, the underlying mechanism for the role of reward remains unclear. There are at least two possible hypotheses for the role of reward in task-irrelevant VPL: a reinforcement hypothesis and an alertness hypothesis. In the reinforcement hypothesis, reward evokes reinforcement signals, which lead to behavioral changes of the stimulus paired with reward (Rescorla & Wagner, 1972). If this is the case, the

stimulus should be predictive of reward and, therefore, precede reward. In contrast, in the alertness hypothesis, alertness increases the probability of prioritized visual information being selected for processing (Posner & Petersen, 1990). Alertness is usually elevated when cues are presented before the stimulus. Thus, if the reinforcement hypothesis is true, VPL should occur only when reward follows stimulus presentation. However, if the alertness hypothesis is true, VPL should occur when reward precedes stimulus presentation. We tested the plausibility of the two hypotheses by manipulating the order of reward and stimulus presentation. Participants were separated into two groups by reward timing: the Before group (n=5) who received reward 400 ms before (n=5) the stimulus presentation, and the After group (n=6) who received reward 400 ms after the stimulus presentation. There were 12 training sessions expanding for 12 days. Prior to each training session, participants were asked to abstain from eating and drinking for 5 hours. In both groups, only one eye was trained (the trained eye) in which two orientations (trained and untrained) were presented in a random order while dynamic noise was consistently presented to the untrained eye to render the orientations invisible. In both groups, the detection performance was measured for two orientations for each eye before and after the 12-day training period. In both groups, there were no performance improvements for the untrained eye. The trained eye showed significant performance improvements in the After group, but not in the Before group. These results demonstrate that VPL only occurs when reward follows stimulus presentation. Therefore, the present study supports the reinforcement hypothesis.

Disclosures: **Z. Wang:** None. **D. Kim:** None. **C. Hu:** None. **Y. Sasaki:** None. **T. Watanabe:** None.

Poster

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Program #/Poster #: 060.02/HH8

Topic: D.07. Vision

Support: DFG SFB 874

Title: Representation of object categories in a non-cortical brain

Authors: ***R. PUSCH**, A. AZIZI, A. SERIR, C. AKMESE, O. GUNTURKUN
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Abstract: Perceptual categorization of objects is a vital process for humans as well as for all other vertebrates. In humans higher order visual and prefrontal cortical areas play a key role in categorization. Birds on the other hand lack these cortical brain structures and have evolved nuclear aggregations instead. On a behavioral level, birds are capable of an astonishing variety of cognitive functions including categorization - despite the absence of a layered cortex. Thus, the

neural fundamentals of these functions are quite invariant to the differences in the anatomical organization of the respective brains. Here we investigate the neuronal mechanisms that guide categorization behavior in pigeons (*Columba livia*). Pigeons were the first non-human animal in which the ability to categorize objects was shown and since then a large body of literature has emerged investigating the behavioral aspects of categorization in these animals. Despite the detailed knowledge of the behavioral processes, their neuronal fundamentals remain poorly understood. In the present study behavioral experiments were complemented with electrophysiological recordings to understand the neuronal foundations of the categorization behavior. We recorded single neurons in two visual areas in the avian forebrain: the entopallium, the first telencephalic recipient area and the mesopallium ventrolaterale (MVL), an associative visual area of the bird brain. During our experiments we presented different sets of stimuli to freely moving and behaving pigeons while recording single cell activity from the aforementioned regions. In our task the birds were confronted with visual stimuli belonging to different categories (cars, human faces, monkey faces and animals). Importantly, the pigeons do not have to categorize these stimuli during our experiments but merely had to peck on each stimulus, irrespective of its content. Thus, instead of training pigeons on predefined categories, we simply presented the stimuli and analyzed the neural output. Despite the absence of a formal categorization behavior of the pigeons, category borders are discernable in the neuronal population code of associative visual forebrain structures of the pigeon brain. In current experiments we test the variability of these category borders. By adjusting reward contingencies during our experiments we hypothesize that the neuronal pattern representing this category will change. Based on our results we compare to what extent neuronal mechanisms of perceptual categorization are shared by different classes of vertebrates.

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Poster

060. Visual Categorization and Learning

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Topic: D.07. Vision

Support: European Research Council grant agreement 339490 “Cortic_al_gorithms”

Title: Neural correlates of iconic memory in primary visual cortex

Authors: ***R. TEEUWEN**, C. WACONGNE, U. H. SCHNABEL, M. W. SELF, P. R. ROELFSEMA

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Abstract: After a briefly presented visual stimulus disappears from a screen, a very accurate representation of the visual information remains accessible to the observer for a short amount of time. This ‘iconic’ memory trace decays very rapidly, over a period of 200-300ms, but during this time window stimulus details can be recalled with great accuracy in accordance with a short-lasting, high capacity memory store. The neural mechanisms that underlie this form of memory are unknown. We hypothesized that the gradual decay of visual activity in primary visual cortex (V1) is a neural correlate of the iconic memory trace. To test this hypothesis we trained two macaque monkeys on a task in which they needed to use iconic memory to mentally trace one of a number of curves. We determined the amount of information in iconic memory by calculating how much extra stimulus time the iconic memory is ‘worth’. This was done by comparing a standard version of the task to a version in which the memory trace was abolished by a mask. The worth is reflected by the amount of extra viewing time that needs to be added in the masked paradigm to achieve equivalent performance as in the non-masked version of the task (Loftus et al. 1992). Our paradigm yielded estimates of iconic memory worth in the same range as earlier reports in humans (60-100ms). We then recorded multi-unit activity in V1 using Utah arrays while the monkeys performed the task, and we established a novel way of computing the worth of iconic memory based on the information present in the lingering V1 activity (i.e. neuronal worth). For both monkeys, the estimates of the worth of iconic memory based on the neural data were highly similar to the estimates based on behavior. Next, we quantified the shape of the decay of iconic memory by presenting the mask at different latencies after stimulus offset. For each latency, we calculated the remaining iconic worth based on behavioral performance and on the neuronal data. Again we found that the results from the behavioral analysis and the neuronal analysis were in good correspondence. Taken together, these results suggest that the decaying activity in V1 after stimulus offset is a neuronal correlate of iconic memory.

Disclosures: R. Teeuwen: None. C. Wacogne: None. U.H. Schnabel: None. M.W. Self: None. P.R. Roelfsema: None.

Poster

060. Visual Categorization and Learning

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Program #/Poster #: 060.04/HH10

Topic: D.07. Vision

Support: MH002032

Title: Combined lesion of inferior temporal areas TE and TEO severely impair visual categorization in rhesus monkeys

Authors: *T. SETOGAWA, M. A. ELDRIDGE, R. C. SAUNDERS, B. J. RICHMOND
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Abstract: Inferior temporal cortex, comprising areas TE and TEO, plays an important role in the integration of visual features into identifiable objects. Our previous studies demonstrated that monkeys with bilateral TE or TEO removals showed only a mild impairment in categorization of visual objects based on perceptual similarity. Here we tested the effect of combined lesions of area TE and TEO. Prior to the TE+TEO removals, three monkeys were trained to categorize morphed images of cats and dogs as “cat-like” or “dog-like” to get reward. The stimuli were morphed (blended and warped) cats and dogs ranging between 0 and 100% dog, with a distribution biased around the category boundary (11 levels, 0, 25, 35, 40, 45, 50, 55, 60, 65, 75, 100% of dog). The monkeys had to touch a bar to initiate trial. Then a test image appeared, followed by a red dot. After 1000 - 3000 ms the red dot turned green for 1000 ms. If the test image was more cat-like, a correct response was to release the bar while the red dot was present, after which a new trial was selected. If image was more dog-like a correct response was to release the bar after the dot turned green, after which the dot turned blue and a liquid reward was delivered. We analyzed the behavioral data collected 10 days before the lesions, and compared this with the data collected 10 days after recovery from surgery. Combined TE+TEO lesions produced a severe impairment in visual categorization which showed only a small amount of recovery across the 10 post-lesion testing days. These monkeys did not show any impairment in a simple visual discrimination task in which the subject had to discriminate two Walsh patterns, nor in a test of visual acuity in which contrast sensitivity was assessed. Thus, combined TE+TEO lesions do not affect low-level vision, but lead to a profound loss of high-level visual categorization in the monkey.

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Poster

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The New Energy and Industrial Technology Development Organization (NEDO)
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Title: Recency of stimulus repetition degrades performance of old world monkeys in sequential delayed visual match-to-sample with visual noise

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Abstract: The neural mechanisms of visual object recognition and short-term memory are often studied using old-world monkeys. Recently in experiments on short-term memory with Rhesus monkeys (*macaca mulatta*) it has been reported that monkeys and humans seem to use different strategies (Wittig et al., 2014, 2016). They reported that rhesus monkeys rely heavily on recency of stimulus repetition to solve visual short-term memory task, whereas humans rely heavily on specific memorization.

Here, we analyzed the behavioral performance from 5 monkeys of two species (2 Rhesus monkeys and 3 Japanese monkeys (*macaca fuscata*)) to determine whether they also used recency in delayed match-to-sample tasks with visual noise. The monkeys were required to fixate while a short sequence of visual stimuli (2-5) was presented. They were required to report whether the test (last) stimulus matched the first stimulus in the sequence by releasing a bar in the primate chair. We added random dot visual noise on the test stimuli to degrade the stimuli patterns (Shidara et al., 2005; Kuboki et al. 2017). We previously found that the behavioral performance of Rhesus monkeys was affected by the amount of visual noise (Shidara et al., 2005; Kuboki et al., 2017). Here the behavioral performance of Japanese monkey was less strongly affected by the amount of visual noise than for Rhesus monkeys. We examined whether there is an effect of recency in this task. The performance of both species was affected by the number of stimuli in the trial. They performed better in shorter trials. In addition, the error rate increased when the matched stimulus in the previous trial was presented as the test stimulus in the current trial. These results seem to show a strong recency effect in a visual recognition task in both species of monkey, an effect unaffected by visual noise on the test stimulus.

Disclosures: **R. Kuboki:** None. **N. Matsumoto:** None. **Y. Sugase-Miyamoto:** None. **B.J. Richmond:** None. **M. Shidara:** None.

Poster

060. Visual Categorization and Learning

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Topic: D.07. Vision

Support: NIH Grant MH116500

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Title: Role of oscillations in encoding visual familiarity

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Abstract: Previous experience can influence the processing of incoming sensory information by the brain and alter perception. However, the mechanistic understanding how this process takes place is lacking. We have discovered that persistent theta oscillations in the mouse primary visual cortex encode information about familiarity and the spatial frequency of the stimulus. The low-frequency oscillations in LFP and single unit activity emerged following perceptual training of animals to one or more visual stimuli of vastly different physical properties. The oscillations required the muscarinic acetylcholine receptors for their induction and expression. Interestingly, detailed analysis of the units revealed distinct neuronal ensembles active at different cycles of the oscillation. Furthermore, these ensembles were located in different cortical layers, leading to a hypothesis that feedforward and feedback projections may play different roles in these oscillations. Recordings in the visual thalamus and the secondary visual areas confirmed this hypothesis. Finally, familiarity-evoked theta oscillations influenced neuronal responses to the oncoming visual information depending on the oscillation phase. Our work demonstrates a new mechanism of visual stimulus feature detection and learning.

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Poster

060. Visual Categorization and Learning

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Program #/Poster #: 060.07/HH13

Topic: D.07. Vision

Title: Selectivity for numerical categories within and without visual receptive fields in primate association cortex

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Abstract: As part of the dorsal visual stream or ‘where’ pathway, neurons in the primate association cortex encode the spatial locations of stimuli, but they also encode more abstract information like rules, reward and importantly, numerical magnitude. Do they do so independently of their location in space? We approach this question by mapping the visual receptive fields (RF) of neurons in prefrontal cortex (PFC) and ventral intraparietal area (VIP). Independently, we recorded these neurons’ activity towards the number of dot stimuli i.e. numerosity shown centrally during a discrimination task. After classifying the visual RFs, we

evaluated neuronal responses to numerosity. We found that in these association areas, neurons were selective for numerosity even when the dot stimuli were presented outside their RFs. While the proportions of numerosity-selective neurons varied according to the RF location, neither the strength of numerosity selectivity, nor the latency to discriminate numerosity varied with the RF location. This indicates that selectivity to abstract numerical categories is largely independent from classical visual receptive fields in PFC and VIP such that information about numerosity is shared similarly amongst neurons with different types of RFs.

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Poster

060. Visual Categorization and Learning

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Topic: D.07. Vision

Support: NIH Grant NIH R01 HD064636
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Title: Non-symbolic exact calculation involves infero-temporal “visual number form areas”

Authors: *M. AMALRIC, A. O'DONNELL, C. LUSSIER, J. CANTLON
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Abstract: The role of the recently discovered “Visual Number Form Areas” (VNFAs) - infero-temporal (IT) regions responding more to Arabic numbers than letters - in mathematical cognition is currently highly debated. The triple code model has hypothesized that such IT regions, interfaced with abstract representations of numbers encoded across formats and modalities in the intraparietal sulcus (IPS), would only recover numerical visual symbols. However, recent results suggest that they can also activate during calculation as well as during advanced math reflection in professional mathematicians in complete absence of visual stimuli, and even in absence of visual experience. Thus, an alternative hypothesis would be that IT regions are not essentially linked to symbols but rather store abstract information about numbers. In the present experiment, we show that even in a fully visual context non-symbolic arithmetic calculation activates IT regions at least as much as symbolic calculation. Functional magnetic resonance images (fMRI) were acquired in 14 young adults. Subjects saw pairs of symbolic arithmetic operations (either 2 multiplications or 1 addition and 1 multiplication) or their non-symbolic counterparts (dot arrays) and had to decide whether they had equal results. To allow fast and exact calculation with dots, we spatially arranged them in subgroups that did not exceed the subitizing range (e.g. 2 groups of 3 dots). Subjects were equally accurate on symbolic and non-symbolic calculation. They were overall faster on symbolic calculation. Within symbolic

and non-symbolic conditions, 2 numerically equal multiplications (e.g. 3×2 vs 2×3) elicited the fastest response, followed by numerically different pairs (e.g. 2×4 vs 2×3 or $5 + 2$ vs 2×3) and finally by numerically equal pairs using different operations (e.g. $4 + 2$ vs 2×3). Thanks to an independent auditory localizer probing brain activations to mental calculation and nonmath semantic judgements, we identified 4 math-related regions of interest (ROIs), including bilateral VNFAs and IPS, in which we performed sensitive statistical analyses at individual level. First, beta comparisons showed more intense and extensive activation in IT for non-symbolic versus symbolic calculation. Second, a representational similarity analysis revealed that activation patterns elicited by symbolic and non-symbolic calculation were highly correlated in our 4 ROIs and that such correlation was not significantly different in bilateral VNFAs compared to bilateral IPS. These results tend to show that IPS and IT regions altogether constitute a core network for storing and manipulating abstract numerical representations.

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Poster

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Topic: D.07. Vision

Support: NIH Grant MH103479

Title: Reinstatement of stimulus specific neural dynamics in human visual cortex

Authors: *B. L. FOSTER, D. YOSHOR

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Abstract: Episodic memory involves consciously remembering past events often with an impressive degree of perceptual detail. How is the brain able to recreate prior perceptual states without the relevant sensory inputs? A long-held view is that consciously remembering a stimulus requires reactivation of activity patterns associated with the perception of that stimulus. Therefore, this theory of 'sensory reinstatement' not only predicts the reactivation of relevant functional neuroanatomy, but also the reactivation of stimulus specific neural dynamics. To test this critical question, we combined high-density intracranial recordings with a novel frequency tagging paradigm to explore the neural dynamics of sensory reinstatement in human neocortex. In order to isolate the reactivation of stimulus specific dynamics, we leveraged prior observations that visual grating stimulus uniquely induce narrow band gamma oscillations (30 - 70 Hz) in primary visual cortex, and that the frequency of these oscillations is contrast level dependent. We therefore designed a paired associates paradigm where auditory tones (300, 700, 1700 Hz) were paired with grating stimuli of different orientations (45, 90, 135 deg.) and contrasts (20, 50

100%). After learning the tone-grating pairs, participants were required to retrieve the associated grating (probed for either orientation or contrast) for a given auditory cue. The use of auditory tones as retrieval cues limited the confound of visual cues, improving isolation of reinstatement dynamics. Two subjects with high-density intracranial recordings from early visual cortex (V1/V2) performed the task with a mean accuracy of 92.5%. During learning, grating stimuli induced clear gamma oscillations, whose peak frequency was higher for higher contrast levels. We therefore asked if these stimulus specific encoding features were reinstated during retrieval. Indeed, during retrieval, we observed the reinstatement of narrow band gamma activity, which differed in peak frequency for each retrieved stimulus, as observed during stimulus encoding. The onset of these reinstatement dynamics was ~400 ms after the presentation of the tone cue, a delay far greater than observed at encoding. Furthermore, these gamma reinstatement dynamics were on average 'sustained' during the retrieval period, reflecting jittered gamma bursting at the single trial level. These findings provide unique electrophysiological evidence of stimulus specific reinstatement dynamics in human neocortex. In addition, our observations have potential links to similar investigations of sensory recruitment dynamics during working memory.

Disclosures: **B.L. Foster:** None. **D. Yoshor:** None.

Poster

060. Visual Categorization and Learning

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Program #/Poster #: 060.10/DP07/HH16

Topic: D.08. Visual Sensory-motor Processing

Support: NIH 1T32-EY021462
NIH R01-EY05729

Title: The dynamics of optic flow during natural locomotion

Authors: ***J. S. MATTHIS**, K. S. MULLER, M. M. HAYHOE
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Abstract: A long history of research on the visual control of locomotion has explored the role of optic flow in the regulation and guidance of human walking, but the optic flow stimulus experienced during natural locomotion has never been recorded. To this end, we used optic flow estimation algorithms to measure head-centered optic flow recorded from the head-mounted camera of a mobile eye tracker. The traditional view of optic flow holds that the Focus of Expansion (FoE) lies in a stable location in the walker's direction of travel. In contrast, our analysis shows that the acceleration patterns of the head during gait cycle cause the FoE to move constantly at very high velocities within the walker's field of. Thus it is unlikely to be useful for controlling heading. In contrast, when we recalculated optic flow in a retinal reference frame, we

found flow patterns that were far more regular than those seen in the head-centered reference frame. Thus it seems unnecessary to “correct” for the effects of eye movements on retinal optic flow in order to recover the FoE in the head-centered optic flow, as has generally been thought. Rather, the gaze stabilization reflexes that allow for fixation during locomotion simplify the visual motion patterns on the retina. Fixation nulls motion at the fovea, resulting in regular patterns of outward flow. This regularization should increase a walker’s sensitivity to the subtle variation of flow velocity and orientation that specify 3D structure-from-motion information. These results therefore cast doubt on the idea that walkers use the FoE to control heading, but suggest a critical role of visual motion information for the perception of the 3D scene structure and a possible role in the control of posture during locomotion.

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Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 061.01/HH17

Topic: D.08. Visual Sensory-motor Processing

Title: Perceived location of a test-flash before, during and after smooth pursuit eye movement is not influenced by the presence of the pursuit target

Authors: ***J. POLA**, H. J. WYATT

Dept. of Biol. and Vision Sci., SUNY Col. Optometry, New York, NY

Abstract: When a person makes smooth pursuit eye movements, background objects appear to remain stable in visual space even though, as a result of the pursuit, the image of the objects shifts across the retina. One account of this stability is that a pursuit extraretinal (exR) signal causes a shift of perceived location relative to retinal locus that cancels perceived background displacement. In recent work (Pola & Wyatt, 2016; 2017) we explored the features of this shift: subjects reported on perceived location of a test-flash presented before, during and after smooth pursuit of a moving target, where the target motion occurred predictably or unpredictably to the left or right. We found a shift of perceived location that started before pursuit, occurred more slowly than pursuit and ended with a magnitude less than that of pursuit, regardless of target motion. Of importance here, the test-flash was always observed together with the moving target. Since perceived location of a test-flash can be influenced by the presence of other visual stimuli (e.g., Dassonville et al., 1995; Honda, 1999; Lappe et al., 2000; Pola, 2007; 2011), it is possible that some features of the shift were a result of the presence of the moving target. Given this, the present study explored perceived location of a test-flash for exceptional subjects who are able to make smooth pursuit movements (i.e., smooth pursuit-like movements) without a moving target. Two conditions were used: 1) the subject made smooth pursuit in the dark in response to a target

moving at constant velocity; 2) the subject made smooth pursuit in the dark without a target. In both conditions, a test-flash (10 ms) was presented at different times before, during or after pursuit, and the subject reported on the perceived location of the flash with respect to a target viewed and extinguished before pursuit onset. By varying test-flash location we determined at each time the target-point-of-subjective-equality (TPSE, i.e., the test-flash perceived to be at the location of the pre-pursuit target) where the difference between eye position and TPSE (EP - TPSE) over time gives the shift of perceived location. The results show that the shift was virtually the same when the subject made smooth pursuit with a moving target or smooth pursuit without a target. That is, in both conditions, the shift began before pursuit, occurred more slowly than pursuit and had a final magnitude less than that of pursuit. This indicates that when a subject makes smooth pursuit to follow a moving target, the shift of perceived location arises from an exR signal whose dynamics are not affected by the presence of the target.

Disclosures: J. Pola: None. H.J. Wyatt: None.

Poster

061. Eye Movements and Perception

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Topic: D.08. Visual Sensory-motor Processing

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Title: V1 neurons sense smooth pursuit eye movements

Authors: G. LI¹, J. SHAO¹, *C. L. BAKER¹, K. E. CULLEN²

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Abstract: How sensory systems discern self-generated motion from real motion is an important outstanding question in neuroscience. However, disparate conclusions have been drawn when comparing V1 responses to saccades or smooth pursuit versus their equivalent retinal motion. A recent study has shown that microsaccades could suppress V1 responses and contribute to the differences between motion in the world and self-generated motion, which clearly expands V1's potential role in visual stability during microsaccades. However previous results have not explored whether smooth pursuit eye movements also dynamically modulate neural responses in primate V1.

Here we used a novel experimental design to study whether smooth pursuit affects responses of

single V1 neurons recorded with tungsten microelectrodes. An awake-behaving cynomolgus monkey performed horizontal smooth pursuit which was elicited by step-ramp target trajectories, randomly chosen between 0, 20, 40 and 60 deg per sec. A drifting grating stimulus was optimized for the neuron's receptive field location, preferred orientation, and spatial and temporal frequency. The grating was projected on a curved screen to maintain a constant visual distance during smooth pursuits excursions as much as 30 deg. By using GPU-supported OpenGL, stimulus distortions generated by the curved screen were corrected online in a frame-based manner at 60Hz. To prevent artefacts from velocity mismatch between eye pursuit and visual stimuli, the position of the drifting grating was determined between each screen frame refresh according to the eye position acquired by a search coil system.

We found that V1 neuronal responses to smooth pursuit exhibited an initial suppression around 100 - 200ms followed by an excitatory peak between 200-350ms. The initial suppression produced by smooth pursuit reached had its greatest effect earlier for an eye velocity of 60 deg per sec compared to 40 and 20 deg per sec. However, there were no differences in the timing of the subsequent excitatory peak across the three pursuit velocities.

Our results indicate that V1 neurons can respond differently to the same (retinal) visual stimulus when the eyes move, which suggests that in addition to the visual stimulus presented in the receptive field, V1 neurons also receive other sources of input which modulate visual responses during smooth pursuit. Such modulation in V1 may play an important role in visual stability during smooth pursuit.

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Poster

061. Eye Movements and Perception

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Program #/Poster #: 061.03/II2

Topic: D.08. Visual Sensory-motor Processing

Support: Grant-in-Aid for Scientific Research (B) (16H0291)
JSPS Research Fellow (17J10497)

Title: Relationship between predictive optokinetic behavior and velocity storage following vestibular neurectomy

Authors: *S. MIKI¹, R. BAKER², Y. HIRATA³

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Abstract: Optokinetic responses (OKR) can be induced by large field visual motion in nearly all vertebrate species. Presentation of a velocity step visual stimulus periodically moving left to

right induces predictive OKR in which horizontal eye velocity starts to decrease before the timing of stimulus direction change (Marsh and Baker, 1997). In goldfish this anticipatory decrease in eye velocity was referred to as a Termination component. In some fish (e.g., goldfish and carp) and some human subjects similar predictive OKR could be acquired while in other fish (e.g., zebrafish and medaka), and some human subjects prediction was absent (Miki et al., 2015; Matsuzawa et al., 2017). All experimental models that acquired predictive OKR presented long lasting optokinetic after nystagmus (OKAN) consisting of alternating slow and fast phases eye velocity in the dark observed after an extended velocity step visual stimulation. By contrast, subjects that didn't acquire predictive OKR showed minimal OKAN, suggesting that the underlying velocity storage mechanism (VSM) plays a crucial role in acquisition of predictive OKR (Miki et al., 2015; Matsuzawa et al., 2017). Several studies have reported that OKAN is completely diminished in either labyrinthectomized or vestibular-neurectomized (VN) animals (Collewijn, 1976; Cohen et al., 1973; Zee et al., 1976). Currently, we carried out vestibular-neurectomy in goldfish to manipulate their OKAN and evaluated the ability to acquire predictive OKR. The superior branch of VIII nerve consisting of anterior and horizontal canals along with utricular fibers was sectioned bilaterally one day prior to experiments, and OKAN was measured after applying a constant velocity (20 deg/s) visual stimulus for 1 min. OKAN duration time in VN animals was found to be much shorter (2 ~ 8 s) than in normal animals (30 ~ 50 s), albeit never completely abolished. After 3-hour visual training with a bidirectional velocity step stimulus (+/- 20 deg/s) at 0.0625 cycle/s, VN animals clearly showed a Termination component but smaller than that observed normally. In addition, the time constant for the build-up of eye velocity after stimulus direction change was much shorter in VN than normal animals, but it shortened to comparable smaller values in both conditions during 3-hour visual training. These results suggest that the presence of the VSM per-se, rather than its long time constant is more critically related to acquisition of predictive Termination component, which appeared to compensate for or facilitate the slowly building-up eye velocity after stimulus direction change at the initial phase of visual training.

Disclosures: S. Miki: None. R. Baker: None. Y. Hirata: None.

Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 061.04/II3

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC Discovery Grant
CFI John R. Evans Leader's Fund

Title: Ocular torsion contributes to rotational motion illusions

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Abstract: Rationale: Torsional eye movements are small rotations of the eye about the line of sight. They accompany every gaze shift and are made reflexively to counteract head tilt about the roll axis. We recently showed that torsion can also be triggered visually and is finely tuned to stimulus properties (Edinger, Pai, & Spering, IOVS 2017). However, it is unclear whether torsion has any functional significance for visual perception. Here we examined the relationship between torsion and perception in the flash-grab effect, a mis-localization illusion in which an object flashed on a rotating stimulus is perceived as shifted in the direction of motion. **Methods:** Human participants (n=15) viewed a circular luminance-modulated grating (24° diameter) that rotated at one of five speeds (25-400°/s), either clockwise or counterclockwise, in front of a dark grey background for 0.5-0.9 s. Rotational motion direction then reversed and the grating rotated in the opposite direction for 0.7 s. Two red dots, aligned with the vertical meridian, were briefly flashed simultaneously on the top and bottom edge of the grating at the time of reversal. Participants fixated in the grating center and reported location of the red dots by rotating the wheel on a trackball mouse to adjust two black reference dots. We recorded 3D eye position, including torsion, with a Chronos eye tracker at 240 Hz. **Results:** All participants consistently perceived the two red dots to be shifted in the direction of after-reversal motion, in line with the flash-grab effect. This effect scaled with increasing rotational speed of the grating, and the illusion magnitude (perceived angle) ranged from 3° for the lowest speed to 15° for the highest speed. Direction of torsion followed the rotational direction of the grating, and magnitude of torsional velocity and accumulative angle increased with increasing rotational speed initially, then saturated at about 200°/s. Importantly, perceived angle was strongly correlated with torsional angle ($r = .50$, $p < .001$) or velocity ($r = .48$, $p < .001$) across observers. **Conclusions:** These findings show a tight link between ocular torsion and the magnitude of a perceptual illusion, indicating that motion processing might be shared for torsional eye movements and perception. In addition, torsional eye movements might modulate perceptual performance by providing additional extra-retinal information about rotational motion.

Disclosures: X. Wu: None. M. Spering: None.

Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

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Topic: D.08. Visual Sensory-motor Processing

Support: NSERC Discovery Grant
CIFAR

NSERC PGS-D Scholarship

Title: Eye and body movements during object interactions in real and virtual worlds

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Abstract: Emerging virtual reality (VR) technology stands to make a lasting impact on human behavioural research. Before this occurs, however, it is important to test whether behaviour in virtual worlds is similar to behaviour in the real world. One critical behaviour to test for this similarity is the distribution of attention, measured via eye movements. Recently, we established a normative dataset for eye gaze during object interactions in the real world (Lavoie et al., 2018). The task emulates moving a box of pasta from a counter-top into a cupboard. Here, we reconstruct the same task in VR and compare eye movements in VR to this normative data set when participants perform the VR mediated task in one of two conditions: 1) a “true-VR” condition where participants used HTC Vive controllers to pick-up the virtual pasta box (by holding the trigger) and release it on the targets (release trigger) and 2) a “haptic-VR” condition where participants interacted with a real pasta-box on real shelves (tracked via motion tracking markers), but their visual experience was entirely virtual. The task was reconstructed in the Unity game engine where we created a virtual room with the same measurements and objects as the real-world room used in our normative dataset. The VR was experienced via an HTC Vive headset running SteamVR. Eye movements were recorded using a PupilLabs 120 Hz binocular camera add-on for the Vive. Finally, body and object movements were recorded using 12 Optitrack cameras. Participants completed 20 trials in both the “true” and “haptic” VR conditions (order was counterbalanced across participants). Following our normative real-world dataset, analysis of the VR eye-movements identified specific areas of interest (AOIs): the participant’s hand/controller, the pasta box and the placement targets. For each AOI, we calculated how many times and for how long it was fixated. In addition, we applied our new measures of eye-hand latency to quantify how much in advance of “grasping” (or “releasing”) an object the eyes arrive (or leave). Preliminary results suggest a high degree of overlap between real and virtual world eye gaze, representing an important first proof in principle for using VR in a variety of human behavioural research.

Disclosures: E.B. Lavoie: None. S.A. Stone: None. J.S. Hebert: None. C.S. Chapman: None.

Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

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Program #/Poster #: 061.06/II5

Topic: D.08. Visual Sensory-motor Processing

Support: DFG D.27.13942

Title: Extra-retinal mechanisms as compensation for retinal-circuit-level visual suppression around saccades

Authors: *S. IDREES^{1,2}, M.-P. BAUMANN^{3,4}, F. FRANKE⁵, Z. M. HAFED^{3,4}, T. A. MUENCH^{1,6}

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Abstract: Visual perception is robustly suppressed around the time of saccades, but the mechanisms underlying such suppression remain controversial. Even though evidence exists for both visual-only and extra-retinal origins of suppression, possible interactions between the two remain unexplored. More importantly, neural loci for visual-only and extra-retinal sources of saccadic suppression are not fully described. Here, using a combination of experimental techniques, we show that a substantial component of perceptual suppression arises from visual-only mechanisms already in the retina, the very first stage in the visual processing cascade. We first asked 8 human subjects to localize a low-contrast stimulus flashed at different times around the occurrence of saccades (~6 deg size). The saccades were performed across a patterned background having 1 of 3 dominant spatial frequencies (randomly chosen from trial to trial). Localization performance was impaired for flashes presented around the time of saccades (saccadic suppression), and the impairment was weakest for saccades across a high spatial frequency background. In separate blocks, we ran the subjects on a similar task without saccades; this time, saccade-associated retinal image shifts were simulated by rapidly moving the background for 70 ms while the subjects maintained fixation. “Suppression” still occurred but lasted significantly longer than with real saccades. Critically, the dependence of suppression on background spatial frequency was identical to that with real saccades. To identify a retinal source for such image-dependence of visually-driven suppression, we used ex-vivo retinal electrophysiology and recorded from >500 retina ganglion cells (RGC’s) in isolated mouse and pig retinae. We matched the experimental conditions of the human simulated saccade paradigm (i.e. with rapid global image shifts and brief probe flashes), and we found that RGC responses to the flashes were also strongly suppressed. Interestingly, the dependence of retinal suppression on background image statistics matched the human psychophysical results, and the RGC suppression lasted even longer (up to ~1000 ms) than in the human experiments. We conclude that both retinal and extra-retinal mechanisms may interact synergistically during saccadic suppression. Retinal circuits may dictate the overall properties of saccadic suppression, including dependence on background image statistics, whereas extra-retinal mechanisms act to dramatically shorten suppression originating in the retina. Such compensation can minimize disruptions to perception associated with prolonged post-saccadic retinal modulations.

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Poster

061. Eye Movements and Perception

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Program #/Poster #: 061.07/II6

Topic: D.08. Visual Sensory-motor Processing

Support: Canadian Institutes for Health Research Grant FDN 354070

Title: Prioritization of visual stimuli in the intermediate layers of the superior colliculus

Authors: *B. J. WHITE¹, J. Y. KAN¹, L. ITTI², D. P. MUNOZ¹

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Abstract: Priority map theory postulates the existence of a dynamic neural map that integrates visual saliency with goal relevance information to systematically prioritize the allocation of attention and gaze. Recently, we reported evidence that the midbrain superior colliculus (SC) plays an important role in visual saliency coding in the superficial visual layers (SCs)^{1,2}. Here, we examined priority coding in the intermediate sensorimotor SC layers (SCi) using a linear microelectrode array (LMA) to record across the layers and examine depth-dependent saliency-relevancy interactions. Specifically, we used a modified version of a previously established task and stimulus to compare the contribution of saliency and relevancy signals in the SCi. Rhesus monkeys (*Macaca mulatta*) were presented with a wide-field array of oriented color stimuli (~200 items) with two salient but feature-distinct oddballs (differing in orientation and color). One oddball was goal-relevant (*salient-relevant*), the other goal-irrelevant (*salient-irrelevant*), and both were embedded in a feature-homogenous array of 'distractors' (*non-salient-irrelevant*). Following the appearance of the array, the animals were required to maintain fixation for a short period (0.5-0.7sec) allowing us to quantify saliency/priority related responses uncontaminated by motor responses. This was followed by the disappearance of the fixation stimulus, which instructed the animal to launch a saccade to the goal-relevant oddball for a reward. We report four main findings: 1) SCi neurons signaled the presence of both oddballs at approximately the same time, ~80ms post array; 2) SCi neurons prioritized the goal-relevant oddball shortly after this, at approximately 105ms post array; 3) The response pattern remained rank ordered throughout the delay period until saccade selection of the relevant oddball (i.e., response remained highest for the *salient-relevant* oddball, lower for the *salient-irrelevant* oddball, and lowest for *non-salient-irrelevant* items); 4) the magnitude of this representation was depth dependent, and centered around the SCi (~1-2mm from the SC dorsal surface). These results are consistent with a priority map in the SCi that combines saliency with relevancy information to systematically rank order stimulus locations for attention and gaze control. **References:** 1. White et al. (2017). Superior colliculus neurons encode a visual saliency map during free viewing of

natural dynamic video, *Nature Communications*, 8, 14263. **2.** White et al. (2017). Superior colliculus encodes visual saliency before the primary visual cortex. *PNAS*, 114, 9451-9456.

Disclosures: **B.J. White:** None. **J.Y. Kan:** None. **L. Itti:** None. **D.P. Munoz:** None.

Poster

061. Eye Movements and Perception

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Program #/Poster #: 061.08/II7

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC

Title: Effects of saccade size and target motion in transsaccadic perception

Authors: ***A. SINCLAIR**, S. L. PRIME

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Abstract: Humans typically make 3-5 rapid eye movements, called saccades, per second to visually explore their environment. During each saccade the image of the world shifts across our retina and yet we still perceive the world as stable. This transsaccadic perception is thought to be accomplished in part by brain processes that spatially update object locations across saccades (Melcher & Colby, 2008). Most transsaccadic perception research has focused on elucidating how and to what extent the brain keeps track of object locations across saccades using simple, static stimuli. Little is known about how our brain keeps tracks moving objects across saccades. Gysen et al. (2002) showed that subjects were more accurate at detecting sudden, unpredictable intrasaccadic spatial displacements of a moving target than a static target. These findings are surprising given the apparent greater complexity in spatially updating a moving stimulus across a saccade compared to a static stimulus. However, in Gysen et al. subjects only made relatively small and orthogonal saccades relative to intrasaccadic displacement direction, which have been shown to enhance intrasaccadic displacement detection with static stimuli (Niemeier, Crawford, & Tweed, 2003). Here, we extend Gysen et al by systematically varying the saccade amplitude and direction to determine how different saccade metrics might influence in accuracy in detecting intrasaccadic displacement of moving stimuli. We also examined the extent to which displacement size and relative post-saccadic location of the motion stimulus might influence detection performance. Subjects were presented with a dot stimulus moving with smooth continuous motion across a display as they maintained their gaze on a fixation point. Subjects were required to make a saccade when the fixation point moved to a different location. On some trials, the dot jumped forward or backward during the saccade. Subjects made a 2AFC response to indicate if they detected a displacement or not. Eye movements were measured using the SMI RED eye tracker (120Hz). We hypothesized: 1) displacement detection rates will decrease as

saccade amplitude increases; 2) detection rates will increase as displacement size increases; and 3) greater detection rates when saccades are directed towards and close to the dot. Our results supported all of these hypotheses. Subjects were most accurate when the saccades were the shortest, the post-saccadic retinal eccentricity of the dot was the smallest, and the displacement was the largest. Our novel findings suggest the same basic processes are involved in transsaccadic perception for both static and dynamic stimuli.

Disclosures: **A. Sinclair:** None. **S.L. Prime:** None.

Poster

061. Eye Movements and Perception

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Program #/Poster #: 061.09/II8

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC
CIFAR

Title: Assessing different 3D gaze vector calibration techniques on synchronized motion capture and eye-tracking data

Authors: ***S. STONE**¹, E. B. LAVOIE², C. S. CHAPMAN²

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Abstract: Collecting synchronized motion capture and eye-tracking data is essential to looking for interactions between action and vision in the real world that move beyond the limits of screen-based tasks. However, to better understand how vision drives action, we must be able to quantify how accurately three dimensional (3D) gaze vectors can be generated. Gaze vectors can be created by regressing the 2D pupil location (i.e. X and Y) to some known target in 3D space. Because the fixation target is known, the model is able to predict the location of future targets in space, and can be subsequently used to map 2D pupil positions to 3D world coordinates. Here, we tested which of five different calibration procedures would produce the most accurate 2D pupil-position to 3D world-coordinate mapping: self-sweep (participant moving wand through entire capture volume in S-shape sweeps), experimenter-sweep (experimenter moves the wand through entire capture volume in S-shape sweeps), area-paint (experimenter moves wand only in small task relevant areas), beep-look (auditory cue to fixate on a stationary target in task relevant area), and stationary gaze (participant rotates head while locking gaze on stationary wand tip). Each procedure took roughly a minute to complete and was completed three times. In four of the procedures, the participants tracked the tip of a calibration wand and in the fifth (beep-look) participants fixated on tracked markers placed at each location. Each gaze vector (five calibrations x three repetitions = fifteen trials) was modeled for each trial type (also fifteen total),

and the average minimum distance between the gaze vector (3D line) and wand tip was calculated. We found that the calibration procedures that explored the most space (e.g. self- and experimenter-sweep, stationary gaze) resulted in better performance than those that focused on task relevant volumes (e.g. area-paint, beep-look). Preliminary results suggest that stationary gaze offers the best performance (approximate average of 35 mm across one minute of data), likely because it allows the participant to explore the working area maximally in a short time frame. This suggests that accurate and highly valid gaze vectors can be created with relatively little data.

Disclosures: **S. Stone:** None. **E.B. Lavoie:** None. **C.S. Chapman:** None.

Poster

061. Eye Movements and Perception

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Program #/Poster #: 061.10/II9

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant R01NS065395
DFG Grant RE 3693/1-1

Title: Interindividual differences in eye movements during face viewing are consistent across task and stimulus manipulations

Authors: ***K. WEGNER-CLEMENS**, J. RENNIG, J. F. MAGNOTTI, M. S. BEAUCHAMP
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Abstract: There is substantial interindividual variability in the eye movements made by humans viewing faces: some participants spend more time fixating the mouth of the viewed face, while others spend more time fixating the eyes. To determine the consistency of these interindividual differences, 41 participants viewed faces while their eye movements were recorded with an infrared eye tracker (EyeLink 1000 Plus, SR Research Inc.). The stimulus was manipulated by presenting either dynamic faces (two-second videos of one of four talkers speaking an audiovisual syllable) or static faces (two-second presentations of still frames from the videos). The task manipulation consisted of requiring subjects to perform either a speech task (reporting the identity of the syllable) or a gender task (reporting the gender of the talker's face). The task manipulation was successful, as evidenced by high accuracy in both tasks (98% for syllables, 97% for gender). Fixations from the period between 150 ms after stimulus onset to 1850 ms after stimulus onset (150 ms before offset) were analyzed. All fixations were subjected to a two-dimensional principal components analysis (PCA). The first PC (PC1) accounted for 42% of the total variation and consisted of a positive peak around the eyes of the talker and a negative peak around the mouth. PC1 values were calculated for each participant, stimulus and task condition

and used as a measure of individual differences in face looking behavior. To assess consistency, we correlated these values (one per subject) across conditions. When performing the same task (gender) on different stimuli (static vs. dynamic) there was very high correlation between PC1 scores: $r = 0.90$, $p = 1.9e-15$. When performing a different task (gender vs. speech) on identical dynamic stimuli, correlation was lower ($r = 0.41$, $p = 0.007$). When performing different tasks (gender vs. speech) on different stimuli (static vs. dynamic) correlation was lower still ($r = 0.26$, $p = 0.18$). These results demonstrate that participants' internal preferences for face viewing interact with the viewed face and the behavioral demands of the task to determine eye movement behavior.

Disclosures: **K. Wegner-Clemens:** None. **J. Rennig:** None. **J.F. Magnotti:** None. **M.S. Beauchamp:** None.

Poster

061. Eye Movements and Perception

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Program #/Poster #: 061.11/II10

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC

CIHR

CFREF VISTA

Title: Convolutional network model of allocentric landmark impact on target localization

Authors: *S. SALIMIAN^{1,2}, R. WILDES^{1,3}, J. CRAWFORD^{1,4,2,5}

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Abstract: The degree to which egocentric and allocentric reference frames are utilized during target localization, is a critical question in dynamic visual processing. For example Li et al (2017) tested their contributions using the cue conflict task on macaque monkeys, where the monkeys were presented with a target and an allocentric landmark. The landmark was then masked and shifted (or not shifted). During the shift paradigm the monkeys' final gaze position was significantly shifted towards the virtually relocated position of the target in allocentric coordinates. In the current work we model these results with a learning-based convolutional network. This model inputs two binary arrays (T1 and T2), where T1 contains the target localized at a particular spatial location as well as an allocentric landmark represented as the intersection of vertical and horizontal lines. In T2, the target is no longer present and the landmark is either shifted or not shifted. The positions of the target and the landmark intersection were determined from the experimental paradigm used in Li et al (2017). The algorithm then

outputs a vector anchored at (0,0) on the array, corresponding to the location where the target has been localized. The ground truths for training the network were set as the final eye position of the macaque as found in Li et al (2017). The network achieves its results through multilayer processing, which begins with two convolutional layers that work to extract features, the resulting output following the convolution layers is sent into a set of two fully connected layers to produce the final location. Following the first fully connected layer, the outputs for both T1 and T2 are concatenated and then passed onto the next fully connected layer. The concatenation works to combine the inputs from the two arrays, separated temporally. The algorithm models the findings in Li et al (2017), thus as the landmark is shifted away from the target, the network's target position is also shifted away from the ground truth in a manner that is modeled after the macaque's eye movements. Future work will focus on analyzing the emergent properties of the network and comparing them to actual neural data, for example in our accompanying abstract (Bharmauria et al. 2018).

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Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 061.12/II11

Topic: D.08. Visual Sensory-motor Processing

Title: Saccade-related remapping helps improve perception during fixation

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Abstract: Humans make 2-4 saccades, or eye movements, per second as they analyze a scene. Since the early visual system is retinotopically-organized, its representation of the scene changes after every saccade. However, the visual system needs to integrate features across saccades to form a temporally-continuous representation of the surrounding world. One hypothesis, called *remapping*, is that a presaccadic prediction mechanism performs feature integration immediately before a saccade. The visual system anticipates the consequences of an impending saccade and predicts where task relevant targets will be in retinotopic coordinate afterward (Duhamel et al., 1992, *Science*). This suggests that feature representations at the two locations may become comingled around the time of a saccade and the integration might be improved by training. However, this has not been directly demonstrated. Here, we use random dot patterns (RDPs) to investigate presaccadic motion integration between current and future retinotopic locations. We developed a psychophysical paradigm adapted from Szinte et al., (2016, *J Neurophysiol*) with four spatially separated RDPs, one of which was randomly cued on each trial. The cued RDP always contained a motion signal for 100ms, and the subjects were asked to report the direction

of motion. On 80% of trials, a second motion signal simultaneously occurred either at the remapped location of the cued RDP or at two other control locations. Subjects performed the task through the interval blocks of fixation and saccade task. The fixation task was identical to the saccade task except the presence of the saccade target (no saccade).

We found that saccade latencies varied considerably between subjects. In the saccade task, subjects with short saccade latencies showed motion integration between the current and remapped location of the attended RDPs. Remapping occurred from the first session onward. In the short latency subjects, the mean rate of increase of performance in remapping trials was constant across sessions. In the fixation condition, summation of the two motion signals did not happen in early sessions but did increase with training only at locations that were remapped during saccade trials. We did not observe any motion integration for subjects with long saccade latency in both saccade and fixation tasks.

Our results suggest that saccadic remapping can act like a teacher that links locations that are subjected to remapping mechanism.

Disclosures: P. Laamerad: None. D. Guitton: None. C.C. Pack: None.

Poster

061. Eye Movements and Perception

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Topic: D.08. Visual Sensory-motor Processing

Support: KAKENHI JP15K16015
KAKENHI JP17H06034
AMED BMINDS

Title: Neural dynamics of recurrent active vision

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Abstract: An active visual exploration using rapid eye-movements (saccade) is essential to efficiently construct the visual world in primates. This behavior requires a recurrent process consists of visual sampling, object analysis, and motor execution. Advances in neuroscience has accumulated a snapshot understanding on how eye-movement is generated or how object identity is analyzed in particular neural structures. However, it remains unknown how spatial and temporal interactions of multiple cortical areas generate sequences of active visual behavior. In the present study, we aimed to capture the interactions of cortical areas underlying the recurrent sequence of active vision. We implanted 96 channel electrocorticographic (ECoG) electrodes

covering the entire hemisphere of a marmoset brain. We recorded ECoG signals while the marmoset viewed naturalistic movies that included rich social and ecological content. The subjects freely scanned the movies and eye position was monitored throughout with head stabilization. First, we analyzed post-saccadic neural activity. In this period, reafferent visual input and new eye-positions drive neural activity. We found smooth transitions of onset latency in the neural activity from early visual areas in occipital cortex to higher visual areas along the temporal lobe. A small portion of the frontal cortex, corresponding to the frontal-eye-field, showed robust post-saccade activity in which latency was similar to mid visual areas. A surprising finding is that there were two patches of cortical region that showed a much faster visual response, even compared to V1. These were the MT complex and superior parietal to dorsal occipital cortex. Secondly, we analyzed pre-saccadic activity which reflected the planning and production of saccade. We found an increasing amount of neural activity toward saccade onset in the frontal-eye-field and regions around the superior parietal cortex, MT complex and STS. Surprisingly, during the time preceding these classically known eye-movement controllers, we found robust neural activity in the temporal pole. Furthermore, we found two adjacent channels that showed quite distinctive peri-saccadic activity where there was robust pre-saccadic activity in the putative FST and a rapid response to reafferent signals in another channel around the putative MT. The present study provides a novel view on cortical neural interactions during naturalistic visual exploration in the primate brain. For future study, we will build a computational model that captures the information dynamics underlying the recurrent nature of primate active visual behavior.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: JST Centers of Innovation (KANSEI)
AMED brain/MINDS

Title: Marmosets and humans robustly show similar saliency-based looking patterns to natural video stimuli

Authors: *R. VEALE¹, C.-Y. CHEN¹, D. MATROV¹, K. ISA¹, K. MIURA², M. YOSHIDA³, T. ISA¹

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Abstract: Previously, it has been shown that the eyes of humans and macaque monkeys are pulled to visual locations that exhibit high visual saliency according to a computational bottom-up model of visual attention, the saliency map model (Itti et al., 2001; Yoshida et al., 2012). However, the extent to which marmoset attention is pulled by bottom-up visual saliency is not known. We analysed data from 2 head-fixed marmoset monkeys engaged in self-controlled free-viewing behavior of short (15 - 60 sec) video clips drawn from a commonly used video corpus (CRCNS-ORIG). The marmosets' eye movements were recorded using an EyeLink remote eye tracking system. For comparison, we also recorded eye movements from 4 human subjects under the same conditions. The degree to which marmoset and human looking was predicted by the saliency map model was estimated using the Receiver-Operating Characteristic (ROC), which compares the number of true positives to the number of false positives when the model is used to predict behavior at different sensitivity thresholds. To correct for center-bias and other individual biases, false positives were randomly drawn from the set of looking locations of the same animal on other trials. Results: Both marmoset and human subjects looked to salient locations at significantly above chance level (0.59 for marmosets, 0.62 for humans). Furthermore, these results held true for a wide range of parameters of the saliency map model, spatial and temporal smoothing of the model, and parameters of eye movement detection. Specifically, none of the following parameters significantly influenced the predictiveness of the saliency map model: 1) the number of levels of center-surround computation in the saliency model (from 2 to 4 levels), 2) smoothing kernels spatially between 5 pixels and 100 pixels, 3) smoothing kernels temporally between 5 msec to 150 msec, 4) how far back in time saliency was measured before an eye movement (between 0 and 150 msec), 5) eye movement detection parameters from 0 deg/sec (i.e. include every time point) to 500 deg/sec (only very fast saccades), 6) minimum eye movement magnitudes from 0 (accept every eye movement) to 2 degrees of visual angle (accept only large eye movements), 7) minimum fixation lengths from 0 to 250 msec. We performed an exhaustive sweep of all parameter combinations. Since looking is highly predicted by the saliency map model over a wide range of (unbiased) parameters, we conclude that the eyes of both marmosets and humans are similarly and robustly drawn towards salient locations. Further experiments are necessary to determine the precise neural mechanisms responsible for this bias (c.f. Veale, Hafed, & Yoshida, 2017).

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Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 061.15/II14

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC
OGS

Title: Impact of allocentric cues on transsaccadic integration of multiple objects

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Abstract: Transsaccadic integration is the ability to retain and synthesize visual information between different stable fixations. In order to do this, the brain must be able to update an internal representation of object locations and features despite relative changes in retinal location produced by saccades several times per second. It is known that humans are able to retain several objects across saccades based on egocentric mechanisms, but it is not known what role allocentric landmarks play in this process. To test this, we compared performance in a transsaccadic integration task (e.g., Prime et al. *Exp. Brain Res.* 2007) with or without the presence of different allocentric landmarks. 1-7 Gabor patches with pseudorandom orientations were presented on a frontal screen while participants fixated a randomized fixation cross. Following a visual mask, participants were required to saccade to a new location and were asked to identify whether a new Gabor patch presented at one of the same locations was rotated clockwise or counterclockwise from the original orientation. **Experiment 1.** In 50% of the trials, a stable cross positioned pseudorandomly within the stimulus array and extending across the screen served as an allocentric landmark and was presented throughout the trial. Using generalized linear mixed modeling (GLMM), results from 9 participants confirmed the expected result that in the absence of allocentric landmarks, performance decreased significantly (from a baseline of ~90% correct) as the set size increased. Importantly, the presence of the cross landmark had a modest but significant effect on this decrease in performance, providing significantly better performance for set sizes of 3 and higher. **Experiment 2.** In 50% of trials, circular ring landmarks occupied the spatial location of the target stimuli providing the visual system with additional spatial location. Results from 9 participants indicate a slight trend toward better performance for some set-sizes, but we did not find a significant effect. **Experiment 3.** To disentangle the effects of these two landmarks, we reduced the set-size to 1 target stimulus in all trials and manipulated the extent of orientation change between fixations in order to plot psychometric functions of orientation sensitivity. Preliminary results from 4 participants indicate that the allocentric cross landmark had no significant effect on orientation sensitivity, suggesting that the effect in Experiment 1 may have been more related to location than orientation. Together, these results suggest that egocentric and allocentric mechanisms combine to provide optimal performance in transsaccadic integration of multiple objects.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: CIHR

Title: The influence of spatiotemporal structure on recall performance in memory-guided saccade sequences

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Abstract: Saccades have been used extensively as a tool to measure cognitive processes such as visual working memory (VWM). The goal of this study was to identify the effect of spatiotemporal structure on performance in memory-guided saccade sequences. Fourteen participants (ages 21-34) were presented with a 5x5 target display encompassing 20°x20° of visual space on a CRT monitor (1280x1024 pixels). The screen continuously displayed a placeholder array outlining the 25 possible target locations, thus providing allocentric cues for target selection in the recall and motor execution phase. Participants were told to maintain fixation at the central crosshair and memorize a sequence of targets presented peripherally. The sequence could have a set size of 3-6 targets. The structure of the sequence could be (1) spatiotemporal (recognizable shape and temporal order), (2) spatial (recognizable shape with random temporal order) or (3) unstructured (random shape, random temporal order). Following offset of the central fixation light, subjects saccade toward the remembered spatiotemporal sequence of targets. Presentation and execution of saccades were done in complete darkness. Preliminary ANOVA results showed significant main effects: (1) recall performance was highest in spatiotemporal conditions followed by spatial only conditions and lowest in unstructured conditions (2) recall performance decreased with larger set sizes. There were also interactions between sequence structure and set size where the benefit of structure was only seen in sequences with four or more targets. Overall, these results show that VWM capacity is improved by the presence of spatiotemporal structure, but this interacts with other factors such as set size.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: RISE GM063787

Title: Mediated relationship of academic issues and oculomotor insufficiency in diverse populations

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Abstract: The Convergence Insufficiency Survey which measures symptoms associated with asthenopia has been shown to be a strong predictor for academic issues pertaining to homework, reading, and grade point average (Chase, 2009). Other research has tied oculomotor insufficiency to academic problems as well, which disproportionately affects underrepresented populations (Basch, 2011). The prevalence of uncorrected refractive error of those in Greater Los Angeles who identify as Hispanic has been shown to be 15.1% (Fisher, 2015). In a previous study we found differing relationships between reports of visual discomfort and academic performance between Latino/Hispanic and Non-Latino/Non-Hispanic populations. Utilizing validated surveys and demographic data we further examined possible differences in subpopulations.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: NIH T32

Title: Neurobehavioral encoding of action intent and organization across development

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Abstract: The performance of complex, goal-directed actions is an essential skill that is developed and refined with continuous practice and careful observation. Tool-use involves the understanding of object affordances, a term used to describe the perception and extraction of object properties that promotes its use. It requires the planning of the immediate task demands along with the planning of subsequent movements that facilitate efficient use of the object. Motor learning during development and even in adulthood relies on action observation to understand the consequence of actions through learned sensorimotor contingences. A variety of studies postulate mapping of observed movements to one's own motor representations through bottom-up mechanisms (i.e., direct matching), while others hypothesize that action understanding involves the identification of goals and subgoals through top-down mechanisms (i.e., teleological stance). However, very few examine these mechanisms in an intricate reach-and-grasp task and through a developmental lens. The aim of the proposed study is to evaluate how action observation affects gaze patterns underlying the organization of complex, goal-directed actions across development. Utilizing eye tracking, subjects across multiple age groups will observe a reach-and-grasp task that either requires a normal or atypical grasp depending on the tool orientation. We hypothesize that participants will form distinct and spatiotemporally organized gaze patterns depending on whether or not the tool orientation requires a normal or atypical grasp. Furthermore, these neurobehavioral patterns will emerge with age. Gaze patterns reveal greater foveal weight towards the object and the operant end of the tool in children regardless of tool orientation or grasp posture. On the other hand, adults' gaze patterns were modulated by tool orientation and grasp posture with more foveal weight directed to the handle tool, a feature rarely attended to in younger age groups but a very relevant aspect of the tool that affords its use. These results support the emergence of tool-object affordances from development to adulthood along with the perception and understanding of action organization that is modulated by tool orientation and grasp posture. Evidence from this study may shed light on the emergence of action organization and the impact of gaze on motor planning and learning.

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Poster

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Empire Innovator Program Scholar Award to S.L.M. and S.MC.

Title: Microsaccade dynamics mediate perceptual alternation in Monet's "Impression, Sunrise"

Authors: ***R. G. ALEXANDER**, A. VENKATAKRISHNAN, J. CHANOVAS, S. FERGUSON, S. L. MACKNIK, S. MARTINEZ-CONDE
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Abstract: Troxler fading—the perceptual disappearance of stationary images, typically in the visual periphery, during prolonged fixation—is counteracted by fixational microsaccades. Whereas microsaccades have been shown to reverse the perceptual fading of contrived stimuli such as Gabor patches, here we demonstrate that their dynamics also contribute to the perception of representational art. This approach can help deepen our understanding of masterpieces such as Claude Monet's "Impression, Sunrise" ("Impression, soleil levant"), in which a red sun rises over two small fishing boats in a port. Whereas the red sun appears perceptually brighter than the surrounding sky, Livingstone (2002) showed that the sun has the same approximate luminance as the surrounding sky. Safran & Landis (1998) moreover noticed that gazing upon a depicted sailor results in perceptual fading of the sun. We set out to assess whether perception of the sun in "Impression, Sunrise" depends on microsaccade production. We collected perceptual reports from 15 human participants while tracking their eye movements. In randomly interleaved trials, subjects either fixated a central target while reporting on the visibility of a peripheral Gabor patch (as in Martinez-Conde et al (2006)) or fixed their gaze on the sailor in "Impression, Sunrise" while reporting on the visibility of the sun in the same painting. Perceptual reports consisted of button presses and releases. To control for contrast adaptation effects across trials, the Gabor patches were presented at eight different compass orientations. In addition, the "Impression, Sunrise" painting was presented both in its original orientation and as a mirror-image (horizontally-flipped) version, such that the sun also appeared in two different spatial locations across trials. Trials were 30 seconds long, and both the Gabor patches and the sun were presented at an eccentricity of 9° (from the center of fixation to the center of the Gabor or sun). We found a tight correlation between microsaccade rates and perception in both scenarios. Microsaccade rates peaked immediately before perceptual visibility reports, and dropped before perceptual fading reports, for both Gabor patches and Monet's sun, with equivalent timing and dynamics in the two cases. This indicates that microsaccade dynamics play a direct role in the perceptual dynamics of Monet's artwork, and that the perceptual vanishing of the sun in "Impression, Sunrise" is due to Troxler fading.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

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NSF 1439189

Empire Innovator Scholar Award to S.M. and S.M-C.

Title: An oculomotor signature as a fraud resistant tool for biometric identity verification

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Abstract: Digitalized interpersonal communication and instant access to data has transformed society, making its citizens more vulnerable to identity theft and cybercrime. Therefore, the need for a hackproof biometric authentication is greater than ever. The characterization of a person's eye movements might provide a foolproof approach to identify an individual, because those movements, made by the living eye, are generated by the brain online and therefore are more difficult to imitate artificially. Moreover, previous studies have demonstrated that eye movements differ between individuals. To study the potential of eye movements as a biometric tool, we characterized the eye movements of 18 participants. Unlike other studies, we also added microsaccades - small eye movements that are generated involuntarily - to the continuum of oculomotor variables that can serve as an oculomotor signature; this resulted in high precision identification of individuals: one-versus-one classification, applying a nearest neighbor algorithm, yielded an accuracy of >99% based upon ~25 minute sessions, during which participants executed a battery of visual tasks such as fixation, visual pursuit, free viewing, etc. When using only a small subset of the data (~3 minutes of a fixation task), the discrimination accuracy remained higher than 97 %. When we further limited the data that we used as input for our classifier, sampling only 30 secs (a single fixation trial), we nevertheless obtained classification accuracy exceeding 94%. Because eye-trackers provide improved spatial and temporal resolution with each new generation, we expect that both accuracy and the minimum sample duration, necessary for reliable oculomotor biometric verification, can be further optimized.

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Poster

061. Eye Movements and Perception

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Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant EY019963

Title: The nigrotectal projection of the mouse

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Abstract: The gabaergic nigrotectal pathway plays a critical role in gating the gaze-related activity present in the superior colliculus. In addition, it is believed to regulate direct connections between the visuosensory, superficial gray layer (SGS) and visuomotor neurons located in the intermediate gray layer (SGI). The development of optogenetic lines in the mouse has resulted in increasing interest in the use of this animal model for oculomotor system studies. Towards this end, we have begun characterizing the nigrotectal projection in C57BL/6J mice. Pressure injections of biocytin were made into the substantia nigra of the mice. These produced anterogradely labeled terminal arbors within the superior colliculus. The vast majority of labeled boutons were found within ipsilateral SGI. The terminal field was present throughout the mediolateral and rostrocaudal extent of the layer, but was otherwise distributed heterogeneously. Specifically, it was much denser laterally and filled the entire layer. More medially, it was densest within the middle of the dorsoventral extent of the layer. In addition, the SGI terminal field displayed a patchy or web-like appearance due to differences in terminal density. Axons could also be seen extending in stratum opticum and these apparently produced a very sparse innervation of ipsilateral SGS. A denser terminal field was apparent in the lateral part of the deep gray layer (SGP). A few biocytin labeled terminal arbors were occasionally observed in contralateral SGI, but these displayed no apparent distributional organization. Thus, the mouse displays a nigrotectal projection that is very similar to that seen in other mammals, with the exception of the fact that the contralateral projection is not heavier rostrally and laterally, like that of the rat. In light of these similarities, we injected the AAV5/hSvn-hChR2(H134R)-mcherry virus into the mouse substantia nigra. This resulted in channelrhodopsin (ChR2) being expressed in nigral neurons and in their terminals within the superior colliculus. Examination of the fluorescent labeling revealed the same terminal field pattern as that observed with biocytin injections. Voltage and current clamp recordings of SGI neurons made from slices of the midbrain in these animals revealed the presence of short latency IPSCs and IPSPs in these

neurons upon photo activation of ChR2 in the nigral terminals. Having demonstrated the effectiveness of this approach, we plan to dissect the effects of activating nigroreticular terminals on different populations within the collicular layers.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: R01EY025172
R01EY021228

Title: Target-feature and outcome histories prime perceptual speed and efficiency in an urgent visual search task

Authors: *E. E. OOR, J. A. SEIDEMAN, T. R. STANFORD, E. SALINAS
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Abstract: The priming of pop-out (PoP) is a psychophysical phenomenon characterizing the role of target feature repetition on search speed during visual search tasks in which the target pops out. Its main manifestation is a decrease in reaction time (RT) for trials in which the pop-out target contains a feature shared with prior trials, versus an increase in RT for trials in which the pop-out target contains a feature that contrasts with prior trials. It is an important phenomenon because in many ways it resembles the actions of attention, but is likely an independent perceptual filtering mechanism. Current descriptions of PoP are based on RT measurements, which represent the composite output of numerous cognitive operations, including motor preparation, perceptual evaluation, attentional deployment, and speed-accuracy tradeoffs. Thus, isolating the effect of PoP upon perceptual evaluation alone is a key step for characterizing its function. To this end, we designed an urgent visual search task, the “compelled oddball” (CO) task, that minimizes extraneous motor factors affecting the subject’s performance. In this task, the target is a red (or green) oddball among green (or red) distracters, and crucially, the probability of a correct choice depends fundamentally on processing time (rPT), or cue viewing time, such that perceptual and motor performance are decoupled. Choice accuracy is tracked as a function of rPT with high temporal resolution, permitting the precise assessment of color and target location repetition effects upon perceptual decision speed and task efficiency (asymptotic performance). In data collected from two macaque monkeys, we find that when target color stays constant for 4 consecutive trials, performance on the ensuing trial sees large improvements in

speed and efficiency when comparing choices where the target is of the same versus the opposite color (68% and 37% correct task efficiency, respectively, with chance being 25%) — while RT varies minimally. Weaker but still significant effects are seen even for single repetitions. Success and RT history are also known to impact perceptual evaluations. We find a visible increase in task efficiency when a given trial is preceded by 4 correct versus 4 incorrect trials, with combined color/success history producing the largest changes overall. In contrast, although fluctuations in motor strategy are evident in success- and RT-history analyses, they occur independently of the perceptual evaluation. With this, we have uncovered strong facilitation and inhibition caused by the PoP acting specifically on perceptual processing speed and task accuracy, independent of additional effects on motor performance.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: R01DC014930 (WZ)
R21EY025550 (WZ)

Title: Modulation of effects of pre-cues on saccade latency by spatial and contextual factors in behaving monkeys

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Abstract: It has been well documented that pre-cueing results in short-term plasticity in visually guided saccade tasks. When the cue is presented in the same location of the target (valid cue), saccade latency is decreased compared to that when the cue is presented in the opposite direction of the target (invalid cue). While this paradigm has been extensively studied over four decades, important knowledge gaps exist in understanding the underlying mechanisms. For example, it is not clear how the cue effects vary for targets between the valid and invalid locations. It is also not clear the extent to which cue validity modulates saccade latency. The present study examined how the pre-cue effects are modulated by target-cue distance (spatial factor) and cue validity (contextual factor) in two behaving monkeys. In the first set of experiments, monkeys were trained to make saccades to visual targets along the horizontal meridian (± 5 , ± 10 , ± 15). In two-thirds of the trials, the target onset was preceded by a brief appearance (50ms) of a visual cue

(80% valid) at ± 10 degree location. Different from previous studies that assessed cue effects by latency differences between valid and invalid conditions, we calculated latency differences between the cued conditions and the no-cue condition. Therefore, we were able to assess benefit and cost effects separately. It has been assumed that reversal of cue effect from benefit to cost takes place at the center location of the visual field, i.e., pre-cueing decreases latencies to targets in the same hemifield of the cue, but increases latencies to targets in the opposite hemifield of the cue. The results, however, rejected the assumption. We found that the location of reversal of cue effect was at 5 degrees in the ipsilateral hemifield. In the second set of experiments, cue effects were measured for cues with different values of cue validity (90%, 70%, 50%, 30% and 10%). The results showed that the benefit/cost cue effects varied with cue validity. In particular, the relationships between valid/invalid cues and benefit/cost effects were reversed when cue validity was 10% compared to that when cue validity was 90%. These results suggested that pre-cue effects on visually guided saccades are modulated not only by bottom-up mechanisms but also by top-down mechanisms. They put constraints on neural mechanisms underlying the pre-cue induced short-term plasticity.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

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NIH 5T32 EY017271-09
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Title: Dynamics of perisaccadic visual remapping in the frontal eye fields

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Abstract: The nature of saccade-related changes in the receptive fields (RFs) of cortical neurons is unclear. But this issue is central to our understanding of active vision, perceptual stability, and naturalistic models of visual behavior. Some of the open questions regarding RF dynamics may be resolved--or new phenomena discovered--by measuring peri-saccadic RFs with higher precision. To accomplish this goal, we presented continuous, full-field visual stimuli (~10 Hz) before, during, and after visually-guided saccades while recording from single neurons in the

frontal eye fields (FEF). The use of continuously presented visual stimuli allowed us to analyze the relationship between visual stimulation and peri-saccadic neuronal activity at a fine timescale and at virtually any arbitrary combination of latency and duration. Consistent with previous results in FEF and cortical area V4, we found neurons whose RFs shifted retinotopically, parallel to the saccade vector. We also found evidence, in some neurons, for a deviation of this shift towards the endpoint of the saccade. The average time courses of both types of RF dynamics were similar, and well delayed after the latency of each neuron to classical RF stimulation. Individual remapping neurons within the "parallel" and "endpoint" classes also spanned comparable ranges of response latency, suggesting relatively independent processing of perisaccadic visual space. To help resolve discrepancies across individual studies, we detail the most common sources of variability and their relevance to measuring peri-saccadic RF dynamics in FEF.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant EY019273

Title: Neurons in FEF that track where you have looked in visual search

Authors: ***J. W. BISLEY**¹, **Z. BOLANDNAZAR**¹, **K. MIRPOUR**²

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Abstract: When searching a visual scene for a target, we tend not to look at items or locations we have looked at before. Based on the psychological literature, it is thought that this behavior is driven by an inhibitory tagging mechanism, often called inhibition of return, that inhibits responses on priority maps to the relevant items. We hypothesized that this inhibitory tagging signal should be represented as an elevated response in neurons that keep track of stimuli that have been examined. We recorded from 231 neurons in the frontal eye field (FEF) of two animals performing a visual foraging task, in which they had to find a reward linked to one of five identical targets (Ts) among five distractors. We identified 38 neurons with activity that was significantly greater to a previously fixated T in their receptive field than to an unseen T. These neurons displayed a similar difference in response when a distractor that had been fixated earlier in the trial was in the receptive field compared to a distractor that had not been examined. The response to a previously fixated object began before the saccade ended, suggesting that this information is predictively remapped. Unlike most FEF neurons, the activity in these cells was

not suppressed during active fixation and had minimal motor responses, supporting the hypothesis that these represent a separate population of neurons in FEF, yet using traditional classifications from a memory guided saccade, they were indistinguishable from the rest of the FEF population. We propose that these neurons track items that have been looked at within the trial and this that tracking is propagated by remapping. We suggest that these neurons could be the source of the inhibitory tagging signal to parietal cortex, where a neuronal instantiation of inhibitory tagging is seen.

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Poster

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Topic: D.08. Visual Sensory-motor Processing

Support: NIH R01EY019273-01

Title: Elucidating the roles of the frontal eye field and the lateral intraparietal area during ongoing visual search

Authors: ***K. MIRPOUR**¹, **J. W. BISLEY**^{1,2,3}

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Abstract: We make nearly three decisions a second about what object to ignore or fixate while visually searching a scene. Many cortical and subcortical areas of the brain contribute in developing this behavior. Among them, the Lateral Intraparietal area (LIP) and the Frontal Eye Field (FEF) have been shown to play a significant role in finding the most behaviorally relevant object in the scene and making a decision to look at it. Neural correlates of many components of visual search have been investigated thoroughly in the context of simplified single step eye movements. Each area exhibits correlations to some sensory-motor elements of oculomotor decisions and many of these are similar between the two areas. However, the division of labor in context of natural free eye movement behavior has not been investigated. Here we address this question by recording 431 (231 FEF and 200 LIP) neurons from 4 animals performing a free viewing visual foraging task. In this task, animals must find a target among five physically identical potential targets (T) and five task irrelevant distractors. To receive the reward, the animal must fixate the target for 500 ms. The objects are arranged such that when the animal fixates one stimulus, another is likely to be in the response field of the single neuron being recorded. We used a statistical encoding and decoding method based on a generalized linear model to analyze the neural code of the two areas. This method enabled us to reduce the

multiplexed responses to basic behaviorally relevant components at the level of individual neurons and predict the response of them to each basic element. When the array of stimuli appeared, the response patterns of the two areas were qualitatively similar. Both represented the behavioral priority of the object in the response field of the recorded neurons. The major difference between the two areas was the dynamic range of responses to behavioral events during ongoing search. LIP neurons represented the behavioral relevance of objects in the response field through each fixation throughout the trial. In contrast, the responses of FEF neurons waxed and waned as if the signals pertinent for search only appeared when the animal had to decide where to go next, at which point the activity predicted behavior far better than LIP. This modulation was driven by the identity of the object at the fovea and the duration of the fixation. We conclude that LIP neurons make a stable map of the visual scene, whereas FEF neurons represent the dynamic flow, making decisions about where and when to go next.

Disclosures: J.W. Bisley: None.

Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 061.27/JJ8

Topic: D.08. Visual Sensory-motor Processing

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Title: Long-term memory of object locations in craniotopic space requires cortical oculomotor proprioception

Authors: *W. ZHANG^{1,2}, S. G. LOMBER⁴, M. E. GOLDBERG³, L. D. SUN¹

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Abstract: In order to have an accurate representation of visual space, the brain has to compensate for the occasional dissonance between the retinal location of a recently vanished object and its spatial location. For objects that disappear immediately before a saccade, the brain uses corollary discharge to remap the visual representation of the object, eliminate the saccade-

induced error, and calculate an accurate saccade trajectory without calculating target position in space in craniotopic coordinates. However, corollary discharge is insufficient to explain the mechanism behind long-term memory of spatial locations (Karn et al. 1997, Poletti et al. 2013). The brain must have access to a craniotopic representation of space that requires afferent ocular proprioceptive signals as well (Poletti et al. 2013). To determine if proprioception is responsible for this more stable representation of target position, we implanted a cryoloop in the right central sulcus to permit the reversible inactivation of the oculomotor proprioceptive region, area 3a, of the somatosensory cortex. We found that after cooling, the monkey could not remember leftward memory targets after 5 or 9 intervening saccades (Zhang et al., Gordon Research Conference on Eye Movements 2017). However, the target positions we used did not allow us to determine if the effect was caused by an error in the retinotopic or craniotopic representation of the target's spatial location. By limiting the final fixation point and target locations we were able to categorize the monkey's memory guided saccades based on the final target location (craniotopic left or right) and the final saccade vector (retinotopic left or right). The four categories are: craniotopic left & retinotopic left (CL-RL), craniotopic left & retinotopic right (CL-RR), craniotopic right & retinotopic left (CR-RL), and craniotopic right & retinotopic right (CR-RR). After inactivation of the somatosensory cortex, the monkey had major difficulties making memory-guided saccades to CL-RL and CL-RR targets, while having no difficulties making saccades to CR-RL and CR-RR. These results show that inactivation of area 3a has a statistically significant effect ($p < 0.05$) on the craniotopic representation of object's long-term memory of spatial locations, and no effect on their retinotopic representation.

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Poster

061. Eye Movements and Perception

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 061.28/KK1

Topic: D.08. Visual Sensory-motor Processing

Support: NIH K08EY023265
NIH P30EY019007
NIH R01EY014978
NIH R01EY017039

Title: Online control of interocular angles is mediated by ocular proprioception

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Abstract: The exact mechanism of the effect of ocular proprioception on ocular alignment in strabismus remains uncertain. A previous study that unilateral deafferentation of ocular proprioception by lesioning the trigeminal ganglion, interocular alignment changed over time (Lewis et al. 1994). However, a later study did not observe the effect when ocular proprioception was bilaterally lesioned (Lewis et al. 2004). They argued that ocular proprioception is a slow calibration signal for the control of interocular angles, but the evidence has remained conflicting until now. We hypothesize that ocular proprioception provides online control of interocular angles. To prove the hypothesis, we unilaterally implanted a cryoloop in the **right** central sulcus next to area 3a of the somatosensory cortex, the final area in the brain where ocular proprioceptive afferents are processed (Wang et al. 2007). Experiments were done in a head-fixed monkey that received reward when fixating on 25 different points distributed on a monitor (lateral most points 25 degrees). We measured binocular eye position during monocular and binocular viewing. We manipulated cortical ocular proprioception by temporarily inactivating Area 3a by cooling. We observed several changes with inactivation: (1) during monocular viewing at the time of the reward the monkey developed an exoshift, where a small but significant increase of the interocular angle was induced, and nearly fully resolved upon rewarming of the cortex; (2) during binocular viewing, a small but significant exoshift was seen to increase immediately at the start of the monkey's fixation to an asymptote one second later at the time of the reward; (3) this exoshift was significant to targets on the **left** (contralateral) side of the monitor, but not to **right** (ipsilateral) sided targets, suggesting a craniotopic effect of ocular proprioception on online interocular angles and strabismus.

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Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.01/KK2

Topic: E.06. Posture and Gait

Support: NIA (R01AG006457, Horak)

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Title: Cognitively challenging exercise is beneficial on executive function in Parkinson's disease

Authors: *S. JUNG^{1,2}, L. KING¹, M. MANCINI¹, P. CARLSON-KUHTA¹, K. SMULDERS¹, N. BARLOW¹, R. MORRIS¹, J. NUTT¹, F. HORAK^{1,3}

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Abstract: Objective To investigate whether people with Parkinson's disease (PD) can improve executive function with cognitively challenging exercise intervention compared to a control intervention of education

Rationale Executive function, defined as a set of higher-order cognitive processes that control, integrate, organize and maintain other cognitive abilities, is often impaired in people with PD. Executive cognitive impairments are often associated with balance impairments. Therefore, rehabilitation interventions for PD should incorporate both physical and cognitive aspects of their disability.

Methods This report is part of a larger, cross-over, randomized, controlled trial design. Forty-nine people with PD with Hoehn and Yahr stages II-IV (35 male; mean age 69.2 ± 6.8 years; mean Hoehn and Yahr stage 2.2 ± 0.7 ; mean disease duration 7.8 ± 5.3 years) were randomized into either a 3 days/week, 6-week exercise (n=22) or a 6-week education (n=27) intervention, followed by the alternative 6-week intervention. The exercise intervention was a cognitively-challenging, group exercise program based on the Agility Boot Camp-Cognition (ABC-C) program for people with PD led by an exercise trainer. The ABC-C program includes 6 stations: (1) fast gait training (2) whole body, big movements, (3) agility course, (4) lunges, (5) boxing and (6) adapted Tai Chi. The education program taught subjects how to live better with PD (e.g. mood, diet, self management, etc.). Subjects completed the Stroop Color and Word Test (Stroop) prior to the interventions (T0), before the crossover into the second intervention (T1), and at the end of the second treatment (T2). Participants were also assessed at baseline on the Montreal Cognitive Assessment (MOCA) as a potential covariate. The mean MOCA score was 25.7 ± 3.5 and years of education was 16.3 ± 1.7 . All subjects signed an informed consent and this research accords with the Declaration of Helsinki.

Results Time to complete the complex Stroop condition improved only after exercise, irrespective of participants' cognitive status at baseline ($p = 0.009$). The mean total time of Stroop in the incongruous condition was 97.7 ± 48.0 (T0), 79.4 ± 26.3 (T1), and 78.1 ± 78.8 (T2) for subjects in the exercise group first and 75.9 ± 27.2 (T0), 87.5 ± 33.1 (T1), and 32.7 ± 38.3 (T2, all in seconds) for subjects in the exercise group second.

Conclusions People with PD can improve the executive function with cognitively challenging, group balance exercise intervention. Future analysis will compare improvements of balance and gait with improvements of cognition and determine potential predictors of responsiveness, including brain imaging.

Disclosures: S. Jung: None. L. King: None. M. Mancini: None. P. Carlson-Kuhta: None. K. Smulders: None. N. Barlow: None. R. Morris: None. J. Nutt: None. F. Horak: None.

Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.02/KK3

Topic: E.06. Posture and Gait

Support: NIH R00 HD078492
PCO Pilot Grant

Title: Cortical correlates of dual-task turning with and without freezing of gait

Authors: *M. MANCINI, V. BELLUSCIO, S. STUART
Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Background. Difficulty turning while walking is common in people with Parkinson's disease (PD) and may lead to significant disability, freezing of gait (FoG), falls and reduced mobility. Turning may be less automatic than straight walking as it requires control of dynamic balance and sequential, whole-body coordination, in addition turning have been related to executive-attentional mechanisms through dual-task paradigms. However, the role of the prefrontal cortex (PFC) during turning and its association with FoG is not clear. Here, we investigated the relationship between PFC activity and turning behavior in PD and elderly control subjects.

Methods. Twenty-four subjects with PD (13 freezers, FoG+, and 11 nonfreezers, FoG-) in the "off" state and 7 healthy control subjects were tested. Subjects wore 3 inertial sensors (1x each shin and 1x waist) and a functional near infra-red spectroscopy (fNIRS) system while turning in place for 2 minutes (alternating 360 degrees to the right with 360 degrees to the left) under single and dual-task (modified AX-CPT) conditions (ST and DT).

Results. No significant differences in FoG Ratio were found in DT compared to ST ($p > 0.05$). However, average turn peak velocity was significantly reduced under dual-task compared to single-task in both FoG+ ($p = 0.01$) and FoG- ($p = 0.04$). Unlike the PD group, healthy controls showed significantly higher PFC activation with dual-task compared to single-task turns ($p = 0.03$). PD, both FoG+ and FoG-, showed a tendency for higher PFC activity with single-task turns compared to healthy controls, but no significant changes between ST and DT ($p = 0.10$). A significant association between the FoG Ratio and PFC activity was found in FoG+ ($r = 0.68$, $p = 0.02$).

Conclusions. Higher PFC activation with single-task turning in PD compared to healthy controls suggests that the PFC may play an important role in turning control in PD. Association between higher PFC activity and greater FoG severity suggests increased cortical compensation is required with greater loss of movement automaticity. Interestingly, dual-task performance

slowed turning without increasing FoG severity, which may indicate that slowing turns is a compensatory mechanism to reduce FoG, likely underpinned by the PFC activation.

Disclosures: M. Mancini: None. V. Belluscio: None. S. Stuart: None.

Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.03/KK4

Topic: E.06. Posture and Gait

Support: DOD Grant: W81XWH-15-1-0620

Title: Sensory weighting in chronic mTBI with vestibular and oculomotor dysfunction

Authors: *L. A. KING¹, L. PARRINGTON², D. A. JEHU², T. HULLAR³, S. KAMPEL⁵, S. STUART⁴, R. PETERKA⁵

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Abstract: Background: Mild traumatic brain injury (mTBI) is known to disrupt balance control and has been linked to abnormal use of the vestibular and visual systems. Peripheral vestibular and oculomotor dysfunction may affect how patients rely on information from these systems. We used a test of central sensorimotor integration (CSMI) to determine the relative contribution of one or more sensory systems to balance in patients with chronic mTBI. **Objective:** To compare Sensory Weight scores in people with chronic mTBI with and without vestibular and/or oculomotor dysfunction (VOD), compared to healthy controls. **Setting:** Oregon Health & Science University and the Portland VA balance and vestibular laboratories. **Participants:** Twenty-six mTBI patients with chronic balance complaints lasting more than 3 months (65% f, age=39.4 ±12) and 24 healthy controls with no history of mTBI, and no VOD (67% f, age=31.8 ±11) participated.

Design: Participants completed a battery of vestibular and oculomotor tests (calorics, cVEMP, oVEMP, VHIT, convergence, and saccades) and were rated as abnormal (n=18) or normal (n=8). All control subjects had normal function. Participants then completed the CSMI test; a test that uses pseudorandom rotations of the surface and/or visual surround to elicit sway. For this analysis we focused on two conditions: surface movement eyes closed, used to assess reliance on the vestibular system, and surface movement eyes open, to assess reliance on both the vestibular and visual system. Difference in Sensory Weight across groups was assessed using a one-way ANOVA. **Main Outcome Measure:** Sensory Weight (W, range 0 - 1). **Results:** A significant difference in W was found between groups for both reliance on the vestibular system,

$F(2,44)=6.269, p=0.004$, and reliance on vestibular and visual systems together, $F(2,45)=5.848, p=0.006$. W was significantly smaller in mTBI with VOD than controls in both conditions (reliance on vestibular system, W mean(SD) mTBI VOD=0.38(0.10), control=0.47(0.08), $p=0.006$; reliance on paired vestibular and visual systems, $p=0.004$, W mTBI VOD=0.62(0.07), control=0.69(0.06)). There were no significant differences between controls and the mTBI group without VOD, or between the mTBIs with and without VOD in either condition ($p>0.05$). **Conclusions:** Differences in sensory weighting occurred only in the mTBI group with measurable VOD suggesting balance problems in mTBI patients without measurable vestibular and/or oculomotor deficits may have different mechanism. Such underlying differences may affect rehabilitation efficacy.

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Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.04/KK5

Topic: E.06. Posture and Gait

Support: Pacific Udall Center, Grant ID: P50 NS062684

Title: Role of sex on cholinergic activity on attention and gait in Parkinson's disease

Authors: *D. MARTINI¹, R. MORRIS¹, T. MADHYASTHA², T. J. GRABOWSKI, Jr⁵, V. KELLY³, K. CHUNG⁶, A. HILLER⁷, C. ZABETIAN⁴, T. MONTINE⁸, J. F. QUINN⁹, F. B. HORAK¹⁰

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Abstract: Recent studies have demonstrated reduced levels of cholinergic activity in people with Parkinson's disease (PD), which has also been shown to be associated with reduced single-task gait speed. The primary aim of this study is to compare the role of sex on measures of cholinergic activity, attention, and dual-task cost (DTC) on gait performance in people with and without PD. Secondly, to determine if there is a relationship between reduced cholinergic activity and reater DTC in men and women with and without PD. Short-latency afferent inhibition (SAI), a physiological index of central cholinergic activity, is being collected to determine if deficits in DTC gait correlate with reduced SAI. Finally, the attention network test

(ANT) is being administered to determine if changes in DTC gait are mediated by changes in attention. For this abstract, we present data collected from 50 male and 22 female participants with idiopathic PD, as well as 10 male and 17 female participants without PD. In addition to the ANT and SAI, we collected measurements of gait speed, stride length, turn duration, and number of steps in a turn during Single Task and Dual Task (continuous reaction time test) walking to assess DTC. We calculate DTC as $([\text{dual task} - \text{single task}]/\text{single task})$ for each gait variable. Both the males (78.05 ± 20.35 , $p=0.01$) and females (79.54 ± 21.54 , $p=0.01$) with PD had significantly worse SAI than the control males (58.69 ± 24.88). On the ANT, males with PD have worse accuracy than all other groups (male PD 0.89 ± 0.17 v female control 0.99 ± 0.01 , female PD 0.98 ± 0.01 , and male control: 0.99 ± 0.01 , $p \leq 0.04$) and worse reaction times than both the female PD (male PD: 810.11 ± 108.77 v female PD: 729.87 ± 82.24 , $p < 0.01$) and male control groups (male control: 706.60 ± 63.52 , $p=0.01$). There were no significant differences between groups for any of the DTC gait variables. However, we observed a relationship between SAI and turn duration DTC ($\rho = -0.33$, $p=0.02$), and between SAI and number of steps in a turn DTC ($\rho = -0.39$, $p=0.02$), but only in the male PD group. This preliminary data provides evidence that reduced cholinergic activity in males with PD is related to impaired gait performance, which may be mediated by attention deficits. The observed distinction between males and females with PD may be part of the reason that mobility disability severity is heterogeneous within a PD population. Males with PD might have greater gait performance benefits from a cholinergic drug used as an adjunct to standard dopaminergic drug therapy. Future investigations should assess the effects of cholinergic agonists on gait performance in males with PD.

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Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.05/KK6

Topic: E.06. Posture and Gait

Support: NIH R00 HD078492
PCO Pilot Grant

Title: Good vibrations: Cortical activity response to tactile cues in Parkinson's freezers and non-freezers

Authors: *S. STUART, G. BOOTH, M. M. MANCINI, 97239
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Abstract: Introduction. Difficulty with turning often presents in Parkinson's disease (PD) and can result in freezing episodes or falls. Cueing strategies can mitigate mobility deficits, but the underlying mechanisms involved in response are unclear. Theories suggest executive-attentional processes, stemming from the pre-frontal cortex (PFC), may play a vital role. This study aimed to evaluate the effect of tactile biofeedback and metronome-like cueing on PFC activity during turning in people with PD.

Methods. PFC activity during walking and turning was recorded in 28 people with PD while OFF medication (MDS-UPDRS: 42.5±13.8, age: 67.3±5.6years, 16 freezers, 12 non-freezers) using a mobile functional near infra-red spectroscopy (fNIRS) device. Inertial sensors objectively measured turns. Participants walked and made a turn (180°, 360°) with and without biofeedback or metronome-like tactile cueing. The primary outcome was change in oxygenated hemoglobin (HbO₂) 6sec prior to and during turning, which is a proxy for cortical activation.

Results. Results demonstrated that PFC activation increased with turning in both groups, with greater activation required for sharper turns (180° vs 360°, $p=.021$). Similarly, both groups reduced activation towards control levels with metronome-like cueing. However, cortical response to biofeedback was significantly different between the groups ($p=.033$). Specifically, PFC activation decreased in freezers with biofeedback, whereas the opposite occurred in non-freezers. Turning metrics did not significantly change with cueing.

Conclusions. These preliminary findings demonstrate that PFC response to biofeedback may differ between freezers and non-freezers. Furthermore, tactile biofeedback or metronome-like cueing may reduce PFC activation when turning in freezers, which may indicate improved movement automaticity.

Disclosures: S. Stuart: None. G. Booth: None. M.M. Mancini: None.

Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.06/KK7

Topic: E.06. Posture and Gait

Support: NIH R01 AG006457
VA Merit I01RX001075

Title: Cognitive function in people with and without freezing of gait in Parkinson's disease

Authors: *R. MORRIS¹, K. SMULDERS¹, D. PETERSON², M. M. MANCINI, 97239¹, P. M. CARLSON-KUHTA, 97239¹, J. NUTT¹, F. HORAK¹

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Abstract: Introduction: Impaired cognitive function is common in Parkinson's disease (PD) with previous studies suggesting cognitive differences between people with FOG (FOG+) and without FOG (FOG-). However, differences in cognitive function have been inconsistently reported within small cohorts. Additionally, cognitive performance has not been associated with an objective measurement of FOG. Therefore, this study aimed to i) assess a comprehensive range of cognitive domains in a large cohort of FOG+ and FOG- and ii) associate cognitive performance with FOG severity using an objective FOG measure.

Methods: 116 idiopathic PD (50 FOG+ [UPDRS III 46.5±13.40], 66 FOG- [UPDRS III 35.7±10.48]) completed a comprehensive cognitive battery. Six domains of cognition were assessed; global cognition, psychomotor speed, set-shifting, response inhibition, working memory and visuospatial. Objective FOG severity was assessed using wearable sensors during 360° turning. To determine differences, a MANCOVA compared domains controlling for age, gender, education and disease severity, $\alpha \leq .01$ was deemed significant.

Results: There were no differences in cognitive domains between FOG- and FOG+; (Psychomotor speed [F=2.93, p=.037], global cognition [F=3.67, p=.058], set shifting [F=1.76, p=.176], response inhibition [F=2.67, p=.051], working memory [F=1.44, p=.232], and visuospatial [F=.167, p=.683]). Additionally, objective FOG severity was significantly different between groups (p<.01) but was not associated with cognitive performance.

Discussion: This is the largest study to assess a comprehensive range of cognitive domains between FOG+ and FOG-. We were unable to replicate findings of cognitive differences between groups, furthermore when using an objective FOG severity score there was no association with cognition.

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Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.07/KK8

Topic: E.06. Posture and Gait

Title: Age-related differences in quasi-stiffness and the kinematics of individual unit sways during quiet standing

Authors: *A. H. VETTE¹, J. BOBET¹, M. O. ABE², K. NAKAZAWA³, K. MASANI⁴

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Abstract: Since falls are a significant cause of morbidity in the elderly, a better understanding of the control of standing posture may help to reduce the number of falls or their severity. The ageing effect of standing posture is often investigated by measuring postural sway during quiet standing. The majority of studies assume a continuous controller and examine body sway as a steady, continuous process. On the contrary, other research efforts have proposed a repetitive, discrete process to be at work. As there are several computational simulation studies proposing such a repetitive, discrete postural control system, experimental analyses describing postural sway as a repetitive, discrete process may help us to better understand the ageing effect in human postural control. In light of these considerations, our aim was to break down postural sway during quiet standing into individual sways, termed unit sways. We hypothesized that the kinematic properties of unit sways during quiet standing differ between the young and elderly. Five ninety second trials of quiet standing with eyes open were collected in 27 young (14 females; age: 27 \pm 5 years; mean \pm standard deviation) and 23 elderly individuals (12 females; 66 \pm 5 years). All five trials were performed on the same day; no other replication was attempted. Since gender differences in the results were small or not significant, all analyses were performed with genders pooled. No blinding was possible. Ground reaction forces and the body's center of pressure fluctuation were obtained via a force plate, and anterior-posterior body sway was captured by measuring the movement of the third lumbar spinous process via a laser displacement sensor. The measurements were then used to determine, for each unit sway, the sway kinematics and estimate the ankle stiffness, called "ankle quasi-stiffness". In total, 25,899 unit sways were obtained. The ankle quasi-stiffness (elderly: 1,286 \pm 313 Nm/rad, young: 981 \pm 296 Nm/rad; $p = 0.0001$) and the maximal velocity of the unit sways (elderly: 4.25 \pm 1.24 mrad/s, young: 3.51 \pm 0.87 mrad/s; $p = 0.007$) were larger in the elderly, whereas the unit sway duration (elderly: 0.67 \pm 0.13 s, young: 0.76 \pm 0.17 s; $p = 0.007$) was larger in the young. Unit sway size was not significantly different between the two age groups ($p = 0.32$). We conclude that quasi-stiffness and some kinematic properties of unit sways during quiet standing differ between the young and elderly. In current work, a previously published model of quiet stance control is used to investigate potential causes for the observed differences.

Disclosures: A.H. Vette: None. J. Bobet: None. M.O. Abe: None. K. Nakazawa: None. K. Masani: None.

Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.08/KK9

Topic: E.06. Posture and Gait

Title: Sensorimotor phenotyping of mild traumatic brain injury and balance: Feature-based behavioral characterization

Authors: *H. M. RAO¹, G. A. CICCARELLI¹, M. NOLAN¹, A. O'BRIEN², G. VERGARA-DIAZ^{2,3}, H. EDWARDS¹, R. ZAFONTE^{3,4}, J. S. PALMER¹, T. F. QUATIERI¹, P. BONATO^{2,3}, R. J. MCKINDLES¹, A. C. LAMMERT¹

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Abstract: Mild traumatic brain injury (mTBI) is pervasive in civilian and military contexts. However, the current standards of clinical evaluations lack the sensitivity to detect lingering sensorimotor impairments following an mTBI. In this study, we hypothesize that provocative sensorimotor perturbations would enable precise detection of mTBI-related balance impairments. Eight healthy controls and ten subjects with mTBI participated in the study. All procedures were IRB approved and subjects provided written informed consent. Experimental sensorimotor perturbations included visual, vestibular, and proprioceptive perturbations. In addition to impulsive perturbations, there were sustained and/or repeated perturbations, which lasted for over a minute in duration. Through the study, marker-based motion capture, electromyography (EMG), and accelerometry of the lower body was recorded. Force plates under the treadmill provided ground reaction forces. Additionally, a series of validated clinical tests were administered to test each subject's cognitive and mobility functions. Given the multimodal physiological data, the features used to quantify both the static and dynamic balance behavior included the spatiotemporal properties of the gait cycle, joint angles, ranges of joint motion, as well as EMG and accelerometry amplitudes and timings. Behavioral characteristics of the control and mTBI populations were compared during baseline standing and walking trials in which no perturbations were applied. The features derived from accelerometry and EMG showed the highest ability to discriminate the two populations, especially during steady walking, yielding an area under the curve (AUC) of 0.93 using a logistic regression classifier. Second, when comparing the features during an impulsive perturbation, the classification yielded an AUC of 0.98. Lastly, when comparing the features during sustained perturbations, the classification yielded an AUC of 0.81. Of the 8 clinical tests performed, the 4 cognitive tests yielded an AUC of 0.87 and 4 mobility tests yielded an AUC of 0.57. These results indicate that assessing balance using provocative sensorimotor tests in conjunction with detailed, multimodal movement data may lead to much higher sensitivity at detecting balance impairment in the context of mTBI compared to current clinical standards. Results of the present study can suggest new clinical assessments based around specific feature/test combinations identified in the present study.

Disclosures: G.A. Ciccarelli: None. M. Nolan: None. A. O'Brien: None. G. Vergara-Diaz: None. H. Edwards: None. R. Zafonte: None. J.S. Palmer: None. T.F. Quatieri: None. P. Bonato: None. R.J. McKindles: None. A.C. Lammert: None.

Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.09/KK10

Topic: E.06. Posture and Gait

Support: Internal funding

Title: Sensorimotor phenotyping of mild traumatic brain injury and balance: Models for mechanism identification

Authors: *G. A. CICCARELLI¹, M. NOLAN¹, H. M. RAO¹, A. O'BRIEN², G. VERGARA-DIAZ^{2,3}, H. EDWARDS¹, R. ZAFONTE^{3,4}, J. S. PALMER¹, T. F. QUATIERI¹, P. BONATO^{2,3}, R. J. MCKINDLES¹, A. C. LAMMERT¹

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Abstract: Mild traumatic brain injury (mTBI) is pervasive in civilian and military contexts, and current clinical assessments are often inadequate for determining the underlying mechanisms of mTBI impairments. This study's purpose is to computationally model the heterogeneity and subclinical symptoms within mTBI and normal subjects.

We propose an individualized, mechanistic modeling approach for static and dynamic analysis of balance and gait. Our framework embeds a mathematical model of the human body within a state feedback control system that has Kalman state estimation with models of visual, vestibular, and proprioceptive feedback. For static balance, we use a three link inverted pendulum, and for dynamic walking we use the RABBIT model from the University of Michigan. Simulated annealing recovers latent parameters (e.g. controller gains) of the model by comparing model predicted with measured data.

We apply this framework to real human subject data. Eight healthy control and ten mTBI subjects gave informed consent for a review board approved protocol. Sensorimotor tests were implemented within MIT Lincoln Laboratory's STRIVE Center that uses a high-end Computer Assisted Rehabilitation Environment (CAREN, Motekforce Link B.V. Amsterdam, Netherlands).

Our optimization framework recovers the proportional gains at the ankle, knee, and hip joint within the static balance model with simulated data with known parameters. In 10 runs of 200 annealing iterations, percent relative error decreases from 400% to a median (interquartile range) error of 22% (56%). When tested on one real mTBI subject and healthy control, we did not find a significant difference between the proportional gains for the mTBI subject as opposed to the control (10 runs/subject, 400 iterations, Mood's median test p-values = 0.18, 1.0, 1.0 for ankle,

knee and hip uncorrected). However, we did find that overall goodness-of-fit was significantly different between the two subjects (chi-squared=16.2, $p < 0.001$). The model fit the mTBI data better than the control.

This work demonstrates sensorimotor phenotyping with the potential to provide mechanistic explanations for behavior. The methodology may lead to individualized treatment of mTBI-related balance impairments.

Disclosures: G.A. Ciccarelli: None. M. Nolan: None. H.M. Rao: None. A. O'Brien: None. G. Vergara-Diaz: None. H. Edwards: None. R. Zafonte: None. J.S. Palmer: None. T.F. Quatieri: None. P. Bonato: None. R.J. McKindles: None. A.C. Lammert: None.

Poster

062. Posture and Gait: Aging, Injury, and Disease I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 062.10/KK11

Topic: E.06. Posture and Gait

Support: NIH K25 HD086276
NIH R21 HD075612

Title: Sensorimotor transformations for balance in patients with Parkinson's disease are temporally precise but spatially diffuse

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Abstract: INTRODUCTION: Although Parkinson's disease (PD) causes profound balance impairments, we know very little about how PD impacts the brainstem and spinal balance sensorimotor networks responsible for balance control. In animals and the healthy young, patterns of muscle activation in response to a sudden loss of balance are created through a sensorimotor feedback transformation driven by multisensory estimates of Center of body Mass (CoM) motion. Temporal feedback about CoM motion is transformed into a precise pattern of muscle activity that stabilizes the body. Here, we hypothesized that in PD, abnormal disinhibition of the same sensorimotor transformation would describe patterns of abnormal muscle activity in both agonist and antagonist muscles. METHODS: We assessed N=28 mild-moderate PD patients (11 female; age 68 ± 9 y; PD duration, 6.6 ± 5.0 y; UPDRS-III "OFF" score 31 ± 10) and N=13 matched Non-PD subjects with translation perturbations. We predicted muscle activation patterns under two different sensorimotor feedback scenarios. First, as shown previously in healthy young adults, muscles were activated as agonists in response to CoM

motion that would stabilize the body (e.g., for ankle dorsiflexor tibialis anterior, CoM motion backward towards the heels). Second, we simulated abnormal disinhibition of balance networks by allowing muscles to activate as agonists or as antagonists (e.g., for tibialis anterior, CoM motion forward towards the toes). **RESULTS:** PD patients exhibited lower peak CoM acceleration ($\approx 3\%$, $P < 0.0001$) and velocity ($\approx 2\%$, $P = 0.01$) than non-PD individuals, generally consistent with “small sway” reported previously. PD patients also had profoundly higher antagonist activity ($146 \pm 94\%$, $P < 0.01$), and lower agonist activity ($-14 \pm 6\%$, $P = 0.03$). Balance-correcting sensorimotor feedback reproduced the precise timing of agonist activation both in PD ($VAF = 0.86 \pm 0.07$) and non-PD ($VAF = 0.86 \pm 0.10$). However, the disinhibition simulated in the second feedback scenario was critical to reproduce abnormal antagonist activation in PD ($VAF = 0.81 \pm 0.08$), which was characterized by significantly higher acceleration feedback than in Non-PD (98% , $P = 0.004$). **CONCLUSIONS:** Abnormally elevated antagonist muscle activity during balance in PD may result from disinhibition of brainstem and spinal balance sensorimotor networks that are presumably under tonic inhibition from the basal ganglia and its downstream targets in the nonparkinsonian state. Better characterization of interactions between the basal ganglia and balance networks could inform improved therapeutic approaches for balance impairments in PD.

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Poster

062. Posture and Gait: Aging, Injury, and Disease I

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Program #/Poster #: 062.11/KK12

Topic: E.06. Posture and Gait

Support: NIH Grant R01 HD46922

Title: Impaired directional perception of perturbations to standing is associated with balance impairment in people with Parkinson's disease

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Abstract: **BACKGROUND AND OBJECTIVE:** In addition to its primary motor features, Parkinson's disease (PD) may also be associated with perceptual impairments. We hypothesized that reduced directional perception of whole-body motion is correlated with balance impairments in PD. We tested 1) whether directional acuity to whole body perturbations during standing was worse in people with PD compared to healthy young adults (HYA), and, 2) whether balance ability as assessed by the Mini-BESTest, a common behavioral outcome measure, was associated

with poor directional acuity during standing among PD patients. **METHODS:** We used a 2-alternative forced choice (2AFC) paradigm in which participants reported whether they perceived pairs of approximately backward support-surface perturbations delivered with a translating platform (displacement 7.5 cm, velocity 15 cm/s, peak acceleration of 0.1 m/s²) to be in the “same” or “different” direction. The first perturbation of each pair was delivered in the backward direction, while the second of each pair deviated to the left or right by a small amount, typically 3°-30°. Discrimination threshold magnitude and threshold left/right asymmetry were determined and compared to existing data of n=11 healthy young adults (HYA). Linear regressions determined associations with clinical variables. **RESULTS:** 15 PD patients were enrolled (age 64.5±6.8 y, 5 female, OFF medications). Overall, PD patients had worse (larger) directional thresholds compared to existing HYA values (PD: 14.5±4.8°, vs. HOA: 10.0±3.4°, p=0.015). Among PD patients, Mini-BESTest scores were strongly negatively correlated with directional threshold values (p<0.01). Based on the recorded data, PD patients and HYA were comparably asymmetric; however, in 7/15 PD patients, thresholds on one of the two sides could not be reliably determined during the testing period, which may further indicate poor directional perception acuity. **CONCLUSIONS:** Perception of whole body motion in PD is impaired compared to that of young individuals. Further, among PD patients, poorer perception of whole body motion is associated with lower balance ability. Moreover, reduced whole-body direction perception could impair the efficacy of compensatory balance strategies that rely on attentional mechanisms that are used by people with balance impairments with and without PD.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.01/LL1

Topic: E.06. Posture and Gait

Support: NIHR Public Health Research programme (13/164/51)
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CES is supported by the Global Brain Health Institute

Title: Is gait associated with hippocampal volume in older adults?

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Abstract: *Introduction:* The hippocampus displays a volumetric decline with ageing, and its role in memory processing and dementia is well established. While poor gait is also associated with impaired memory and increased risk of dementia, the association between hippocampal volume and gait control remains uncertain. The aim of this study was to examine the association between hippocampal volume, cognition, and spatial-temporal gait parameters in older community-dwellers. *Method:* Eighty-one older adults free of neurological illnesses (mean age 76 ± 6.8 years, 64% women) underwent brain MRI scans and assessments of gait, executive function and memory. Hippocampal volumes were quantified from T1-weighted MRI using automated software. Walking speed, cadence and stride length were measured over a 10-meter walk at self-selected pace, using an inertial measurement unit. A computerised test of spatial and visual memory was used to measure relational memory and executive function was assessed through the Flanker and 2-back tasks. Partial correlations were used to determine the associations between gait, cognition and hippocampal measures, controlling for age, gender and BMI. *Results:* Hippocampal volume was not associated with any gait parameter (all $p > 0.05$). After adjusting for age, gender and BMI, gait speed was positively correlated with performance on the 2-back task ($r = 0.24$, $p = 0.016$), but not memory. Cadence and stride length were not related to measures of cognition. *Discussion:* In contrast to previous reports, we did not find evidence of an association between spatial-temporal indices of gait and hippocampal volume. On the other hand, the observed association between gait and a measure of executive function, but not memory, is consistent with previous reports indicating a stronger association between gait and executive function than between gait and other cognitive domains.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.02/LL2

Topic: E.06. Posture and Gait

Support: The Elsass foundation

Title: The feedforward motor programme during toe walking is impaired in children with cerebral palsy

Authors: ***J. LORENTZEN**¹, **M. WILLERSLEV-OLSEN**², **H. M. LARSEN**¹, **S. F. FARMER**⁴, **J. NIELSEN**³

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Dept. of Neurosci. & Movement Disorders, Inst. of Neurology, Univ. Col. London, London, United Kingdom

Abstract: In order to ensure optimal stability of the ankle joint at ground impact during voluntary toe walking in adults feedforward control of ankle muscles is used. In this study, the maturation of voluntary toe walking in typically developed (TD) children and TD adults was investigated and compared to involuntary toe walking in children with cerebral palsy (CP). 28 children with CP (age 3-14 years), 24 typically developed (TD) children (age 2-14 years) and 15 adults (mean age 30.7 years) participated in the study. During walking on a treadmill walking electromyogram activity (EMG) was measured from the Tibialis anterior (TA) and Soleus (Sol) muscles together with knee and ankle joint position. Low step-to-step variability of the ankle joint position after ground impact found in adults was correlated with low TA and high Sol EMG, which was initiated around 80 ms prior to ground contact. An age-related decline in TA EMG amplitude was found in TD children reaching an adult level at 10-12 years of age. A broad peak EMG-EMG synchronisation (>100 ms) associated with large 10 Hz coherence between antagonist muscle activities was found for the youngest TD children. This, however, declined with age and at the age of 10-12 years where an adult pattern was observed. This reduction in coherence was closely related to improved step-to-step stability of the ankle joint position. Children with CP generally showed lower EMG levels than TD children and larger step-to-step variability in ankle joint position. In contrast to TD children, CP children showed no age-related decline in TA EMG amplitude. Motor unit synchronization and 10 Hz coherence between antagonist EMGs was observed more frequently in children with CP when compared to TD children and in contrast to TD subjects there was no age-related decline. We conclude that TD children as they age develop mature feedforward control of ankle muscle activity. In contrast to this children with CP continue to co-contract agonist and antagonist ankle muscles when toe walking. Development of the corticospinal tract and efficient gating of sensory input may be responsible for the observed changes in ankle joint control in TD children. The co-contraction activation pattern maintained when toe walking in children with CP is possibly due to weak muscles and insufficient motor and sensory signaling necessary for optimization of feedforward motor programs. These findings are important for understanding of the pathophysiology and treatment of toe walking.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.03/LL3

Topic: E.06. Posture and Gait

Support: R01 NS088679

Title: Asymmetry during gait initiation differentiates people with parkinson's disease with and without rem sleep without atonia

Authors: *M. N. PETRUCCI¹, A. L. KOHUT-JACKSON², S. L. AMUNDSEN HUFFMASTER¹, M. E. LINN-EVANS², M. J. HOWELL¹, P. J. TUIE¹, C. D. MACKINNON¹
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Abstract: Postural instability and gait dysfunction (PIGD) are common debilitating symptoms of Parkinson's disease (PD). Progressive neurodegeneration in locomotor regions of the brain stem, especially the pedunculopontine nucleus (PPN), is believed to be a significant contributor to the development of PIGD. Dysfunction of the PPN is also linked to rapid eye movement (REM) sleep behavior disorder (RBD), which is characterized by elevated muscle activity during REM sleep (REM sleep with atonia, RSWA+). People with PD and RBD often have a more rapid disease progression and are more likely to develop a phenotype that is dominated by medication resistant PIGD and falls. The purpose of this study was to test the hypothesis that anticipatory postural adjustments (APAs) and step execution during gait initiation are abnormal in people with early PD and RSWA+, compared with those with PD and normal REM sleep (PD-RSWA-) and matched controls. Forty-eight participants (14 healthy matched controls, 16 people with PD-RSWA-, 18 PD-RSWA+) performed twelve trials of self-initiated (uncued) gait (6 trials starting with the right leg, 6 with the left leg). Amplitude and timing of ground reaction force (GRF) and center of pressure (COP) data were analyzed and compared between groups and limbs (right vs. left and more vs. less affected limb determined by MDS-UPDRS III scores) using repeated measures ANOVAs ($p < 0.05$). The time to peak APA magnitudes (GRF and COP) were significantly longer in the PD-RSWA- participants when the first step was initiation with the less affected leg compared to participants with PD-RSWA+ ($p < 0.009$), while time to each toe-off was longer than controls ($p < 0.022$). No significant differences were observed between the PD-RSWA+ and control groups. Contrary to our hypothesis, the participants with early PD and normal REM sleep muscle tone showed abnormalities in the timing of APAs and step execution when the most affected leg was the initial stance limb. These findings demonstrate that early PD without RSWA is associated with asymmetric neurodegenerative changes in systems that contribute to the timing of APA and step generation, suggesting the time course and expression of PIGD changes are distinctly different between those with and without RSWA.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.04/LL4

Topic: E.06. Posture and Gait

Support: FAPESP/Brazil (Grant 15/02404-7)

Title: Additional haptic information provided by light touch reduces postural sway more than does the anchor system in older adults

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Abstract: Approximately 30% of older adults aged 65 or more fall at least once a year. Different approaches have been considered to minimize the balance deficits that come with aging. One way to attenuate balance deficits is to provide additional sensory cues. The *light touch* (LT) paradigm has been largely used to investigate the effect of additional haptic information on balance control. Another convenient and simple tool that provides haptic information is the *anchor system*. With the anchors, an individual holds a flexible cable in each hand, with a small mass attached at the other end. The individual is then asked to keep the cable taut, and to allow the mass, or weight, to rest on the ground at each side while pulling it along. The present study investigated how each of these two paradigms of haptic contact affects balance performance in older adults, with and without histories of falls. Forty-four older adults participated in this study and were subdivided into two groups: *non-fallers* (n=22) and *fallers* (n=22). Older adults who suffered at least one fall in the last six months were considered as fallers. They fell 2.6 times, on average, in the last six months. They were asked to stand for 35s in feet-together position on a force platform. They performed under four task conditions: (1) non-contact condition (NC), (2) lightly touching a rigid surface with the tip of the index finger of the dominant hand (LT), (3) anchor hand (AH), and (4) adapted anchors, with the cable tied to the tip of the index finger (AF). In both anchor conditions (3 and 4), both hands were used as contact points. The results of the MiniBESTest, which measures functional balance, were higher ($p < .0001$) for the non-fallers (26.0 ± 2.2 points) than for the fallers (19.4 ± 3.5 points). For the postural sway measures based on the center of pressure displacement, the MANOVA showed main effect only for task condition for all variables ($p < .0001$). There was no group difference or any interaction involving groups. The univariate tests showed that the effects were present in the AP and ML directions ($p < .0001$). For the root mean square (RMS) and mean sway speed (MSS), AH and LT reduced postural sway and its speed in comparison to the NC condition, in both directions. LT resulted in lower

RMS and MSS than AF and AH, in both directions. RMS was the only variable that showed that AF reduced postural sway as compared to NC, but only in the AP direction. Overall, both AH and LT paradigms diminished postural sway, but LT provided better use of haptic information than did the AS.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.05/LL5

Topic: E.06. Posture and Gait

Support: R.K. MacDonald Fund for Parkinson's Research
McDonnell Foundation

Title: Beat perception ability and familiarity with music alter gait in older adults during auditory cueing

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Abstract: People have a natural tendency to move along with music, and listening to music can regulate movement patterns. This regulation is the basis for Rhythmic Auditory Stimulation (RAS), a therapeutic strategy using rhythmic properties of music to regulate atypical gait patterns (most commonly in Parkinson's disease or stroke patients). During RAS, users synchronize their footsteps with the musical beat in the stimulus, often improving spatiotemporal parameters of gait, such as stride length, speed, and variability. In healthy younger adults, gait outcomes during RAS are influenced by both familiarity and groove (i.e., desire to move) levels of the stimuli, and these effects appear to interact with beat perception ability. To date, however, these factors have not been examined in older adults - the age group to which gait intervention is most relevant. Therefore, this study investigated how familiarity, groove, and beat perception ability influence spatiotemporal gait parameters in healthy older adults when walking with and without instructions to synchronize to stimuli.

45 healthy older adults over age 50 were randomized to either synchronized or free-walking instruction conditions. Baseline data was collected from an initial, silent walking trial (8 continuous lengths of a 16 ft. sensor walkway). Participants then completed 2 cued walking trials in the following 5 cueing conditions (10 trials total): high familiarity/high groove, high familiarity/low groove, low familiarity/high groove, low familiarity/low groove, and metronome.

Trial order was randomized and all stimuli were adjusted to be 15% faster (in beats per minute) than participants' baseline cadence (steps per minute). Finally, beat perception ability was assessed using the Beat Alignment Test.

Preliminary analyses indicate that low groove versus high groove cueing led to slower strides with significantly greater double-limb support time. Additionally, a familiarity by beat perception interaction indicated that poor beat perceivers shorten their strides when walking to unfamiliar stimuli, and good beat perceivers do not. Good beat perceivers instead exhibit a slowed stride time with low familiarity but not high familiarity stimuli. No significant effects were observed for instruction type (Synchronize vs. Free-Walk). These findings indicate that cues perceived to be low in groove and familiarity may negatively impact gait patterns among older adults during RAS. Additionally, the spatiotemporal parameters impacted by low stimulus familiarity may depend, in part, on one's beat perception ability.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.06/LL6

Topic: E.06. Posture and Gait

Support: National MS Society Grant pilot grant

Title: Optical flow perturbations to detect preclinical balance impairment in people with multiple sclerosis

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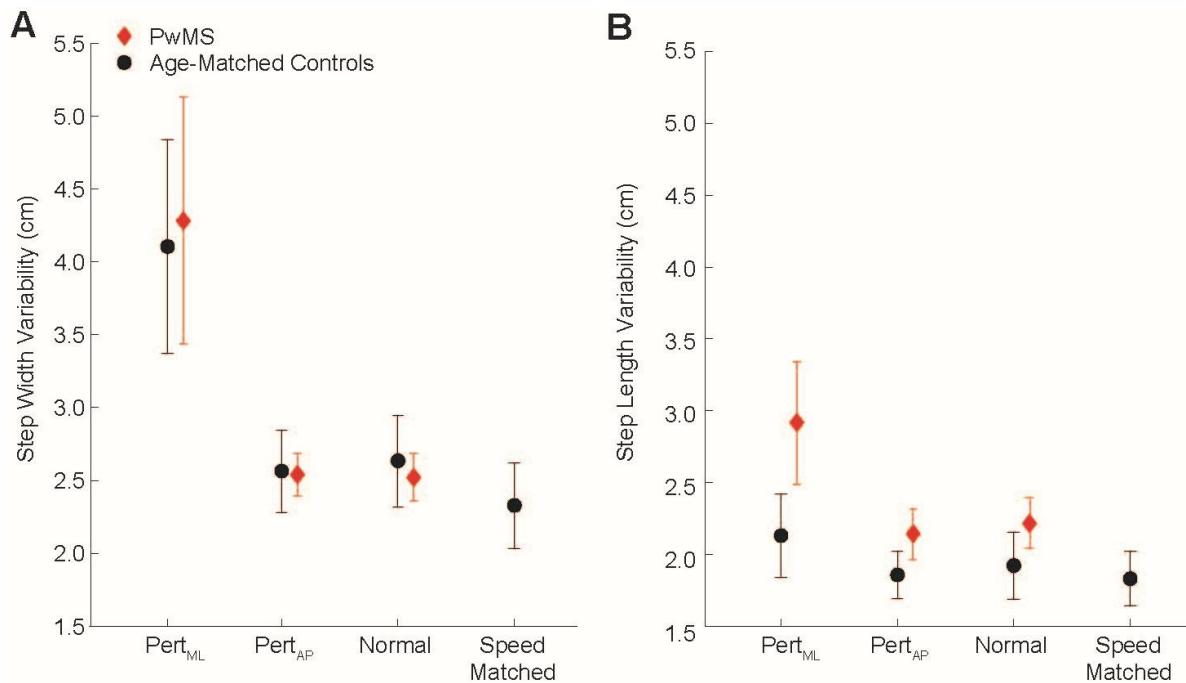
Abstract: Prior to reporting even moderate disability, people with multiple sclerosis (PwMS) are already twice as likely to fall as the general population. In addition, PwMS have an increased reliance on visual feedback for balance control. Thus, optical flow perturbations that elicit the perception of falling may be an effective means to detect preclinical balance impairment in PwMS. As a first step, we are testing the effects of optical flow perturbations on static and dynamic balance control in PwMS and age-matched controls. We hypothesized that, compared to controls, PwMS would increase foot placement (i.e., step length and width) variability more in response to optical flow perturbations in walking. We also hypothesized that perturbations would have a larger effect on dynamic balance control in walking than on static balance control in

standing, the latter quantified using center of pressure variability.

Six PwMS (1 male, 34.7 ± 7.7 years old) and six age-matched control subjects participated in this IRB-approved study. Subjects walked on an instrumented treadmill in a virtual reality hallway. The virtual hallway was perturbed continuously in mediolateral (ML) or anterior-posterior (AP) directions during standing and preferred speed walking.

Differences between PwMS and controls were negligible for unperturbed standing and walking. In contrast, both groups increased step width and step length variability in the presence of ML perturbations. However, consistent with our first hypothesis, these effects on step length variability were larger for PwMS than age-matched controls. Consistent with our second hypothesis, center of pressure variability was similar between groups during standing, even in the presence of perturbations. Our results suggest that perturbations that elicit the visual perception of falling during walking may identify preclinical balance deficits in PwMS that may go undetected during standing.

Figure 1. Gait variability ($n=5$) during normal walking vs. with ML (Pert_{ML}) and AP (Pert_{AP}) optical flow perturbations. Controls also matched the speed preferred by PwMS.



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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Title: Identification of vestibular impairment in schwannoma patients relative to healthy controls requires testing during more challenging gait tests, while vestibular loss following surgery alters standard gait

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Abstract: A wide range of functions, from basic reflexes to high-level behaviors, depend on the vestibular system. By sensing head motion and then generating the appropriate reflexes, the vestibular system is vital for maintaining balance and stabilizing gaze. Using clinical measures, it has been shown that following unilateral vestibular loss, patients experience dizziness, headache, and impaired balance, postural, and gaze control. However, to date, much less is known about the effects of vestibular loss on voluntary behavior. Here, we assessed whether locomotive behavior can predict clinical measures in a group of patients with a diagnosis of vestibular schwannoma (VS) before and after primary surgical resection of their tumor via suboccipital craniotomy and retrosigmoid approach with sectioning of the vestibular nerve. Head movements were recorded during Functional Gait Assessment (FGA), which include 10 gait tasks, using a six-dimensional motion sensor (3-axis linear acceleration and 3-axis gyroscope) in (1) healthy volunteers and (2) acute patients before and six weeks after surgery (3) chronic unilateral vestibular patients. We computed measures of gait speed, asymmetry, and variability during FGA and then compared these with multiple clinical outcome measures including; dizziness handicap inventory (DHI), activities-specific balance confidence (ABC), Beck anxiety inventory (BA), FGA score, postural sway, and vestibulo-ocular reflex gain. First, comparison of patients prior to surgery with controls revealed similar gait measures during standard walking, however patients showed significant differences for more dynamic gait tasks such as those that required changes in walking speed or claiming stairs. Next, comparison of patients before and six weeks after the surgery, revealed a reduction in head movements variability during standard surface-level walking following the unilateral vestibular loss. Interestingly, this reduced variability was correlated with multiple clinical measures. Specifically, patients with more reduced variability had lower anxiety and dizziness scores. Taken together, these results show that variability during standard gait test can identify changes following unilateral vestibular loss in vestibular schwannoma patients. Moreover, testing using more challenging gait tests can be used prior to surgery to identify vestibular impairment in schwannoma patients relative to healthy controls.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.08/LL8

Topic: E.06. Posture and Gait

Support: NIH/NICHD R01HD083314

Title: Effect of abrupt and varied pelvis force perturbation on dynamic balance during locomotion in humans with spinal cord injury

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Abstract: Lateral balance control plays a crucial role during locomotion in humans with spinal cord injury (SCI). Current balance training paradigms in humans with SCI primarily focus on standing or sitting balance, which may have limited transfer to walking. It's unclear whether we could improve lateral balance in humans with SCI by applying a lateral force perturbation during walking. We hypothesized that applying a lateral perturbation force at the pelvis during walking would provide additional challenges to humans with SCI, and the lateral balance would be improved after force perturbation training. Fifteen subjects with SCI participated in the study. Subjects walked on a treadmill in two sessions with a 10-minute sitting break inserted between two sessions. Each session consists of 1-minute of walking with no force, i.e., baseline, followed by 9-minute of walking with either abrupt or varied (the range of variation was 70%) perturbation force, and 2-minute of walking with no force. A custom designed cable-driven robotic system was used to provide a controlled perturbation force (peak magnitude was 8-12% of body weight, duration was 400ms) in lateral direction starting from heel strike of each leg. Ankle and pelvis positions were recorded using custom designed position sensors. The margin of stability (MoS) at the moment of heel contact (MoS_HC), and minimal MoS value (MoS_PK) during stance phase were calculated and were used to quantify the proactive balance and reactive balance, respectively. Repeated-measures ANOVA was used to evaluate the change in MoS within session. The MoS_PK significantly decreased during the early adaptation period for both the abrupt and varied load conditions ($p < 0.001$, $p = 0.003$, respectively), and significantly increased following the release of perturbation force during the post-adaptation period for both the abrupt and varied load conditions (abrupt: $p = 0.005$; varied: $p = 0.027$). Further, the retention of aftereffect showed different patterns between the two load conditions during the post-adaptation period. Specifically, the de-adaptation of the MoS_PK for the abrupt load condition was slower than that for the varied load condition ($p = 0.018$). In addition, the MoS_HC increased at the end of adaptation for the abrupt load condition only ($p = 0.02$). Results from this study

suggest that humans with SCI may adapt to the perturbation force applied to the pelvis and show an aftereffect with increased reactive lateral balance. Further, the pattern of perturbation force had impact on the retention of the aftereffect. Results from this study may be used to develop a force perturbation paradigm for improving dynamic balance in humans with SCI.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Topic: E.06. Posture and Gait

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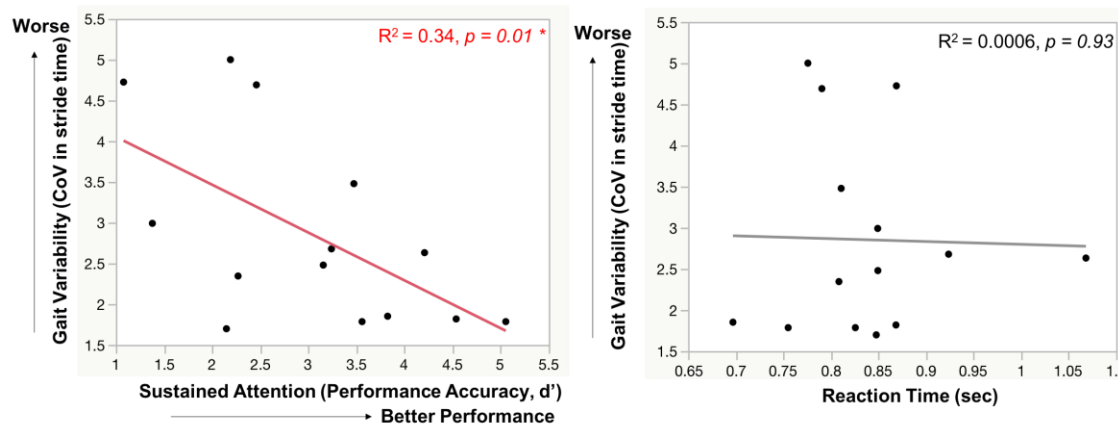
Title: Gait variability and sustained attention are associated in healthy older adults

Authors: *O.-Y. LO^{1,2,3}, A. LUDINGTON², L. A. LIPSITZ^{1,2,3}, M. ESTERMAN⁴, M. A. HALKO⁵, B. MANOR^{1,2,3}

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Abstract: Unsteady gait and cognitive decline often occur concurrently in older adults, yet the link between gait and cognition remains largely unclear. Gait variability is a quantifiable and clinically-meaningful metric of locomotor control that reflects the degree of temporospatial variance in consecutive walking strides. On the other hand, sustained attention is a critical cognitive function that can be measured by the accuracy on continuous performance tests. Previous work by our group has separately demonstrated that gait variability and sustained attention are linked to de-coupling between the dorsal attention and default networks of the brain. However, whether these motor-dominant and cognitive-dominant behaviors are linked to each other is unknown. Gait variability and sustained attention were assessed in 15 healthy older adults (age: 72.6±5.5 years, 5M10F). Gait variability was defined as the coefficient of variation in stride time as recorded by wearable movement sensors. Sustained attention was defined as performance accuracy (d') on the gradual-onset continuous performance task (gradCPT). Gait

variability and sustained attention were correlated ($R^2=0.34$, $p=0.01$), controlling for age and sex. Gait variability was not correlated, however, with reaction time within the gradCPT ($R^2=0.0006$, $p=0.93$), suggesting that this gait metric was related more to attention than speed of motor processing. Together, these results indicate that older adults with elevated gait variability tend to have worse sustained attention. The observed relationship between these motor- and cognitive-dominant behaviors also provides evidence that they may be linked by a common underlying cortical mechanism; namely, the relationship between the dorsal attention and default networks.



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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Program #/Poster #: 063.10/LL10

Topic: E.06. Posture and Gait

Support: UNLV Intramural Faculty Opportunity Award

Title: The influence of transcranial direct current stimulation of the motor cortex on balance in Parkinson's disease

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Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has been shown to improve motor performance of the upper limbs in Parkinson's

disease (PD). However, research is mixed on the ability of tDCS to improve lower limb motor function in gait and balance tasks, especially in tasks not done concurrently with tDCS (transfer tasks). Therefore, the purpose of this study was to determine the influence of tDCS applied during a gait training program on balance performance in PD. The study was a double-blind, sham-controlled, between-subjects experimental design. Twelve individuals with PD were allocated to either a tDCS group or a SHAM stimulation group. Each participant performed 9 training sessions over a 2 week period involving a gait training on an instrumented treadmill with online visual cues of stride length. In addition, anodal tDCS or SHAM was applied over the leg motor area of the motor cortex contralateral (dominant hemisphere) to the primarily affected leg. TDCS was applied at a current strength of 2 mA concurrently with the gait training for a duration of 20 minutes. SHAM stimulation was applied in the same manner according to well-established blinding procedures in which the current was ramped up and down over a 60 second period. Balance performance was assessed using computerized dynamic posturography of the Sensory Organization Test (SOT) in 4 testing sessions that occurred at baseline, the end of training (EOT), and at 2 (EOT+2) and 4 (EOT+4) weeks after training had ended. The primary outcome measures were the 6 equilibrium scores associated with the SOT along with the composite and 3 sensory system scores (somatosensory, visual, and vestibular). The primary outcome measures were analyzed with 2 *Group* (tDCS, SHAM) x 4 *Testing Session* (Baseline, EOT, EOT+2, EOT+4) repeated measures ANOVAs. For the somatosensory score, there was a significant *Group x Testing Session* interaction ($P = 0.003$), which indicated that somatosensory scores were higher for the tDCS group in the EOT testing session. However, post hoc analysis of the interaction just failed to reach statistical significance ($P = 0.061$). For all the remaining variables, the main effects for *Group*, main effects for *Testing Session*, and *Group x Testing Sessions* interactions were all non-significant. The greater somatosensory score for the tDCS group observed 1 day after the gait training and stimulation sessions may indicate that tDCS lead to an increased reliance on the proprioceptive system with a concomitant decreased reliance on the visual system in PD. However, this alteration in the control of balance did not result in an overall increase in balance performance in PD.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Topic: E.06. Posture and Gait

Support: NIH Grant R37NS090610
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Title: Combining learning mechanisms to improve walking in people with stroke

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Abstract: Gait dysfunction is a common cause of mobility disability and restricted independence after stroke. Recent rehabilitation research has developed innovative ways to improve gait patterns. For example, split-belt treadmill walking has shown considerable potential for improving step length symmetry in people with stroke. Unfortunately, improved walking patterns acquired through this adaptation learning-based therapy tend to decay rapidly, particularly if followed by over ground walking. Reinforcement is another mechanism through which new movement patterns can be learned. During reinforcement, a person learns by exploring the optimal movement in response to binary feedback about movement success or failure. While new movements are formed more slowly in reinforcement learning paradigms, they tend to be resistant to decay. Here, we tested whether combining adaptation and reinforcement learning paradigms leads to longer-lasting improvements in over ground walking in people with stroke, relative to locomotor adaptation or reinforcement learning protocols alone. Individuals with chronic stroke were exposed to three learning conditions, assigned in a random order. These conditions included: 1) adaptation plus reinforcement (split-belt treadmill walking followed by walking over ground with reward signals), 2) adaptation alone (split-belt treadmill walking followed by walking over ground *without* reward signals), and 3) reinforcement alone (*tied-belt* treadmill walking followed by walking over ground with reward signals). In reinforcement conditions, a pleasant auditory cue provided a real-time reward signal each time the participant stepped symmetrically. We compared the peak step length symmetry achieved and the duration of symmetrical stepping during over ground walking, across conditions. Preliminary results show that combining adaptation learning with reinforcement signaling often leads to longer lasting improvements in step length symmetry during over ground walking. However, some individuals appear to derive more benefit from adaptation-only or reinforcement-only protocols. This work suggests that rehabilitation could be structured in an individualized way to capitalize on the most effective motor learning mechanisms in order to prolong improvements in over ground walking in people with stroke. Moreover, this approach might also be applicable to rehabilitation training in other domains (i.e. upper extremity, speech, balance) as well as for other neurological patient populations.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Topic: E.06. Posture and Gait

Support: Croatian Ministry of Science and Education, grant 108-1081870-1877
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Title: Gene polymorphisms linked to myelin lipid metabolism and antioxidative pathway may contribute to cerebral palsy etiopathogenesis

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Abstract: In spite of improved maternal, obstetric and neonatal care there has been no significant change of the cerebral palsy (CP) prevalence around the world, which indicates a contribution of non-recognized genetic factors in CP pathogenesis. Complexity and heterogeneous clinical presentation of CP is related to different spatial/temporal distribution of immature brain injuries and abnormal brain development. Neuroimaging studies showed that white matter injury is the most common finding in CP. Integrity of white matter depends on many factors, including regulated metabolism of specific myelin lipids and ability of myelin to respond to oxidative damage. The rationale of this study is based on the following facts: first, demyelination may be associated with altered degradation and accumulation of sulfatides, abundant lipids of oligodendrocyte membranes; second, prenatal or postnatal hypoxia/ischemia is considered as one of the most important factors in CP pathogenesis, and may lead to destruction of white matter; third, glutathione detoxification pathway is common cellular antioxidative protection system; fourth, decreased antioxidative capacity is shown in CP. We investigated a potential combined effect of selected candidate gene polymorphisms in CP. For that purpose, in 67 CP patients and 231 healthy individuals, we estimated frequencies of: (a) two most common mutations in arylsulfatase A (ASA) gene responsible for ASA pseudodeficiency (ASA-PD), a condition associated with lower ASA enzyme activity and reported in several neuropsychiatric disorders; (b) two glutathione S-transferase P1 (GSPT1) polymorphisms shown to be involved in diseases characterized by various levels of cellular oxidative damage. We did not find significantly different frequencies of ASA-PD mutations in CP vs. controls. Interestingly, ASA enzyme activities were in lower range in more than 70% of CP patients, due to unknown genetic or epigenetic factors influencing ASA catalytic properties. In the case of C341T GSPT1 polymorphism, we found significantly higher frequency of the mutated T allele in

CP vs. healthy subjects (6% vs. 27%, $p < 0.05$, chi-square). Also, we didn't find any homozygous TT genotype in CP while in healthy subjects its frequency is 8%. Higher frequency of C341T mutation in controls may indicate its protective role, and contribute to more efficient antioxidative capacity by glutathione S-transferase pathway in healthy individuals. In conclusion, genes related to cellular antioxidative protection and myelin integrity and metabolism seem to be promising candidates for studying genetic factors involved in complex etiopathogenesis of cerebral palsy.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Topic: E.06. Posture and Gait

Support: NSF IGERT grant DGE-1069104

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University of Minnesota Neuromodulation Innovations (MnDrive)

Title: Closed-loop gait phase modulated deep brain stimulation in Parkinson's disease patients

Authors: *C. LU¹, K. H. LOUIE², J. C. GUZIOR¹, T. I. NETOFF², S. E. COOPER¹

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Abstract: Background: Continuous deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus pars interna (GPi) is effective for most Parkinson's Disease (PD) motor symptoms but does not adequately treat gait impairments. Disruptions to the naturally occurring oscillations within the basal ganglia may be restored with continuous DBS, or potentially make it worse. Activity within the basal ganglia has been shown to be associated with the phase of gait and stimulation applied during certain phases may better entrain the oscillations and regularize it compared to continuous delivery. Timing stimulation delivery to specific gait phases, however, is challenging due to system latencies of real-time gait detection. Therefore, the aim of this study was to examine the effect of event-timed DBS on treadmill gait in people with PD. We developed a gait phase stimulation system that estimates and delivers stimulation at the next occurrence of different gait events (ipsilateral heel-strike (IHS), contralateral heel-strike (CHS), or contralateral toe-off (CTO)).

Methods: Five PD patients with bilateral DBS (STN or GPi) were tested in the off-medication state. The participants walked on an instrumented treadmill under three closed-loop stimulation conditions: IHS, CHS, CTO and two control conditions (continuous stimulation at their clinical settings and no stimulation). Treadmill speed was set to each participant's pace (75 to 100% of

overground walking speed during continuous stimulation). The real-time gait detection component was composed of two wireless force sensitive resistors placed bilaterally underneath the foot with accelerometers placed bilaterally on the shank. The stimulation delivery was programmed via the Medtronic Nexus-D interface to control patients' existing implanted neurostimulators. Time interval between closed-loop stimulation delivery and related gait events was estimated. Step length was computed for all conditions as well.

Results: No adverse events were reported during closed-loop conditions by all participants. Our preliminary system was able to deliver stimulation with the gait phase for 56 to 64 percent of gait events. Furthermore, 73 to 88 percent of gait events occurred within 75 ms of stimulation delivery.

Conclusions: Stimulation delivery timed to different gait phases, each with different latency characteristics, is technologically feasible. The delivered stimulation is tolerable and does not show any obvious detrimental effects on gait.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.14/LL14

Topic: E.06. Posture and Gait

Title: Gait parameters of Ts65Dn mice are impaired vs. age matched WT's

Authors: *L. VER DONCK, M. MELIS, H. VAN CRAENENDONCK
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Abstract: *Background:* Alzheimer related pathology is known to increasingly affect cognitive functioning in humans, but has also been reported to be associated with changes in posture control (Sheridan & Hausdorff, 2007) and gait parameters (Moon et al, 2016). *Objective:* To evaluate the effect of developing amyloid pathology on gait parameters in a mouse model APP over-expression.

Methods: Male and female Ts65Dn mice (n=11) and age matched wild type litter-mate controls (n=7) aged 8-9 months were used (JAX). Animals were first trained to walk spontaneously and fluently along the walkway (70 cm long, 10 cm wide) of the CatWalk™ setup (Noldus, The Netherlands). The home cage was mounted at the end of the walkway as a target zone. Mice were food deprived overnight and Dustless Precision Pellets (Bioserv, USA) were provided in

the home cage as a bait to motivate the mice to walk down the walkway. Animals were given maximally 5 trials until a fluent walking performance was obtained. Footprints were recorded with a high speed digital camera and images were analysed using the CatWalk™ software to calculate gait parameters. Data were analysed using 1w-ANOVA (InVivoStat 3.6.0.0). P<0.05 was considered to indicate statistical significance.

Results: Significant changes in gait parameters were detected between Ts65Dn and WT mice: a significant reduction was observed in front and/or hind paws for Initial contact (sec; time of first contact of a foot with the plate since recording started), Max contact (sec; duration of maximal contact), Print width and length (mm) and area (mm²) of the entire foot print, Max area (mm²: print area during Max contact), Stand (sec; duration of contact of foot with plate), Swing (sec; duration of no contact with plate). An increase was observed in Stride length (mm; distance between subsequent placings of foot) and Swing speed (m/s; speed during Swing), while no differences were found for Intensity (8 bit; grey value of all pixels at Max contact), Paw angle (degr; angle of foot axis vs longitudinal line), Duty cycle (%; stand relative to total cycle time of a step); Max contact at (%; duration of Max contact relative to stand) and Stand index (m/s; speed of loss of contact from the plate).

Conclusion: The data show that 8-9 mo old Ts65Dn have increased contact time but reduced contact area with the walkway, indicating abnormalities in their step pattern. These changes can be exploited to test efficacy of novel therapeutics targeting the amyloid cascade.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.15/MM1

Topic: E.06. Posture and Gait

Title: Tremor responses for persons with pd is exacerbated by standing posture

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder of the basal ganglia that results in gradual decline of dopaminergic neurons and leads to problems with the control of movement. One distinct motor problem associated with PD is the emergence of enhanced tremor. This study was designed to assess the impact of changes in postural position (i.e., sitting vs. standing) on bilateral tremor responses for healthy elderly persons and patients with PD. Bilateral tremor was recorded from the hand and finger segments using a series of lightweight uniaxial accelerometers. Frequency, regularity (using Sample Entropy, SampEn) and coupling

(coherence) analyses were performed on the tremor signals. When seated, tremor for the PD patients was more regular (i.e. lower SampEn) and characterized by a single, high amplitude frequency peak located between 4-6 Hz. In contrast, the postural tremor for the older adults was more complex, with low amplitude peaks at 2-4 Hz and 8-12 Hz. For the coupling analyses, all persons exhibited low coherence values between the tremor in the right and left arms. The adoption of standing posture significantly affected the tremor for both the older adults and the PD patients, with increases in both amplitude and regularity observed for all persons when they switched from sitting to standing position although no change in the tremor modal frequency was noted. Further, the increases in tremor were observed without any significant changes in the coupling between upper limbs. Overall, the tremor for the PD persons was greater in amplitude, more regular and resonated at a lower average frequency compared to healthy controls. While the transition from sitting to standing altered the amplitude and regularity of tremor within a given segment, it did not change coupling of tremor between the limbs. This latter result supports the general premise for the independent generation of bilateral tremor with both normal aging and PD. Together our findings support the general premise that the deterioration of the neural oscillators in the basal ganglia have widespread effects on tremor frequency and regularity. However, moderating mechanical factors such as posture can have significant impact on tremor dynamics within a single limb.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Program #/Poster #: 063.16/MM2

Topic: E.06. Posture and Gait

Title: Walking balance control is delayed in Parkinson's disease: Preliminary results

Authors: *D. GRENET¹, H. REIMANN², T. D. FETTROW¹, E. D. THOMPSON^{4,1}, J. J. JEKA³

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Abstract: Parkinson's disease (PD) is associated with an increased risk of falling. We know that people with PD are less stable when standing and walk with a typical gait pattern of short, rigid steps. However, we do not currently understand how balance mechanisms may be impaired in PD during walking.

In healthy walking, a person's immediate response to a balance perturbation is to activate ankle musculature and modulate the center of pressure beneath the stance foot, which propels the center of mass in the opposite direction to the perceived fall. The person will then place their

next step toward the direction they feel they are falling.

Here we present preliminary data from two male subjects with idiopathic PD. Both subjects had motor UPDRS scores of 33 and their disease progression was assessed to be at Hoehn and Yahr stage 2. Subjects walked on a self-paced, instrumented treadmill facing a large curved screen. A scene projection onto the screen formed an immersive virtual environment in front of the subject. The viewpoint and optic flow of the projection matched the head position and walking speed of the subject on the treadmill, such that the subjects' visual input was as if they were walking through the projected scene. The visual stimulus was a roll rotation of the projected scene to the left or right at 25 deg/s² for 600 ms beginning at heelstrike. The scene remained rotated at 4.5 deg for 2 s and then reset to its original orientation at constant speed over 1 s.

We did not observe modulation of the center of pressure in either subject during the initial step following the stimulus, nor did we observe significant modulation of the placement of the first step following the stimulus. Both subjects exhibited a response to the stimulus early in the second step by modulating their center of pressure and accelerating their center of mass.

Bipedal locomotion is inherently mechanically unstable, and so immediate and appropriate motor responses to any balance disturbance are vital to prevent falls. The apparent inability of people with PD to respond immediately to a balance perturbation may contribute to the high risk of falls associated with this disease.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

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Program #/Poster #: 063.17/MM3

Topic: E.06. Posture and Gait

Support: This research was supported by a donation to the Brown Institute for Brain Sciences

Title: A novel method for repeatable tap tests in a rodent model of hydrocephalus

Authors: *D. L. POETA¹, T. K. JACOBSON¹, A. IOANNOU¹, P. M. KLINGE², R. D. BURWELL¹

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Abstract: Normal pressure hydrocephalus (NPH) is a cerebrospinal fluid (CSF) disorder resulting from abnormal CSF circulation and its accumulation in the ventricles of the brain. The accumulation of CSF results in enlarged ventricles (ventriculomegaly) and damage to surrounding brain tissue. NPH patients exhibit cognitive impairments including memory and

attention problems, as well as motor deficits such as short shuffling steps and wider stance (reviewed in Peterson et al. 2016). Currently, the only treatment for NPH patients is a ventriculoperitoneal shunt, which relieves pressure in the brain by draining excess CSF from the ventricles. While shunting is fairly successful in treating cognitive and motor impairments, the mechanisms by which it works are unknown.

A spinal tap test is commonly used to predict a patient's outcome to a shunt prior to surgery. Clinical observations have shown an improvement in gait characteristics post-tap test such as increased stride length and stride velocity (Stolze et al, 2000). In a previous study, our lab established a rodent model of hydrocephalus and observed gait and memory impairments consistent with those seen in human patients. In the current study, we developed a method to conduct repeatable tap tests in our NPH model and analyzed gait characteristics before and after CSF withdrawal.

Adult male Long Evans rats received either a sham surgery (n=3) or kaolin injection via the cisterna magna to induce hydrocephalus (n=3). A closed catheter system (PinPort by Instech) was unilaterally implanted into the lateral ventricle during the same surgery. A tap test was performed on anesthetized rats every two weeks for three months. Rats were tested on a gait analysis task at various time points before and after each tap test. Preliminary results show increased stride speed and decreased stance duration in NPH animals post-tap tests. When compared to NPH animals without a PinPort implant (n=10), there was a significant difference in stride length, stride speed, stance duration and stance to swing ratio. We hypothesize that the tap test decreases the intracranial volume of CSF and decompresses the extracellular space. This allows for increased neurotransmitter communication between neuronal circuits and, as a result, improvement of motor function. We will continue to investigate this effect using electrophysiological recordings to study oscillatory activity across target brain regions.

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Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.18/MM4

Topic: E.06. Posture and Gait

Title: Entrainment of stepping frequency in chronic stroke survivors on a vertically oscillating treadmill

Authors: ***S. C. RAAB**¹, B. ROBERTSON-DICK³, D. GOBESKI², T. ONUSHKO², L. REIM², A. S. HYNGSTROM¹, B. D. SCHMIT⁴

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Abstract: Entrainment of motor synchronization to a sensory input has shown to be an effective rehabilitation technique for treatment of altered gait in many neurologically injured populations. Previous research suggests that individuals with stroke will subconsciously synchronize their stepping frequency to an aurally or visually oscillating source while other studies have shown that subconscious motor synchronization to a sensory oscillator promotes walking activity that is more representative of unimpaired walking. Little research exists that explores the use of an oscillating environment to provide proprioceptive feedback that mimics vertical center of mass oscillations during the gait cycle. The purpose of this study was to quantify stepping frequency entrainment in chronic stroke survivors on a vertically oscillating treadmill. Eight participants with chronic stroke walked on a treadmill vertically oscillating at a frequency that matched each participant's preferred stepping frequency. Amplitudes of oscillations were kept constant. All participants showed intermittent stepping frequency synchronization. On average, subjects synchronized their stepping frequency to the vertical oscillations of the treadmill 36.29 (28.14)% ($p=0.008$) of the time. Each period of synchronization contained on average 8.1 (16.9) steps on the paretic side and 14.5 (35.4) steps on the nonparetic side, although these results were not statistically significantly different from each other ($p>0.05$). These results suggest that individuals with stroke can adapt their stepping frequency and that this type of protocol may be useful in developing rehabilitation methods for improving gait in chronic and, potentially, acute stroke survivors.

Disclosures: **S.C. Raab:** None. **B. Robertson-Dick:** None. **D. Gobeski:** None. **T. Onushko:** None. **L. Reim:** None. **A.S. Hyingstrom:** None. **B.D. Schmit:** None.

Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.19/MM5

Topic: E.06. Posture and Gait

Support: NSF Grant 1563454
CLEAR Grant

Title: Influence of altered neuromechanics via stance time visual feedback on the lateral control of balance of transfemoral amputees walking with a powered knee prosthesis

Authors: ***A. BRANDT**, H. HUANG
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Abstract: Postural control is considered a complex motor skill required for locomotion, and researchers have observed a correlation between impaired individuals' ability generate symmetric motor patterns and to control their balance. In particular, transfemoral amputees exhibit large gait asymmetries by relying more on their intact limb and report a greater number of falls compared to able-bodied people. Lower limb amputation leads to considerable biomechanical changes as well as neurophysiological changes that play important roles in postural control. In contrast to traditional passive prostheses, powered prostheses can mimic biological joint motion, providing fewer biomechanical constraints; yet, amputees still rely more on their intact limb compared to their amputated limb. Are amputees constrained to an asymmetric behavior to maintain balance with a powered prosthesis during walking, or is this altered motor pattern learned and reinforced with a passive prosthesis and preventing more symmetric behavior enabled by a powered device? In this study, we aimed to answer this question by asking 5 amputees to walk with more time on a powered prosthesis and quantifying their resulting motor responses to maintain balance. Strategies of postural control change with the individuals' task and goals, so we controlled subjects' walking speed on the treadmill (self-selected) and used visual feedback targets (amputated limb stance time) to specify the subjects' goal. All subjects trained with the powered knee until primary outcome measures did not differ when subjects walked with and without the Stroop test (attention associated with reweighting visual information). Preliminary results indicate that when provided the higher target (i.e. greater amputated limb stance time), one subject increased stride time by 7%, decreased intact limb stance time by 6%, and improved stance time symmetry by 4% compared to baseline. Further, the subject widened his step width by 12% and widened the distance between the extrapolated CoM and COP by 8% on the amputated side and 16% on the intact side, compared to baseline. In accordance with previous studies, the latter balance measure was greater on the amputated side. These preliminary results suggest improved gait symmetry of amputees may compromise their lateral balance during walking, even with a powered knee prosthesis. Researchers developing advanced prostheses with greater functionality and clinicians encouraging gait symmetry may benefit by additionally monitoring lateral balance measures during walking for further assessment of prosthesis and amputee user performance.

Disclosures: **A. Brandt:** None. **H. Huang:** None.

Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.20/MM6

Topic: E.06. Posture and Gait

Support: Department of Veterans Affairs Grant #O1435-P
Research Career Scientist Award #F7823S (Patten)

University of Florida Graduate Student Fellowship (Banks)

Title: Cortical inhibitory/excitatory balance during dynamic plantarflexion scales with walking speed

Authors: *C. L. BANKS, V. L. LITTLE, Q. DING, C. PATTEN
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Abstract: Short-interval intracortical inhibition (SICI) is a GABA_A-mediated phenomenon often used to probe inhibitory brain circuits related to motor control. Similarly, intracortical facilitation (ICF), probes excitatory circuits putatively mediated by glutamate. These paradigms are typically measured at rest or during isometric contractions, thus it is unknown how SICI and ICF are modulated with respect to each other during dynamic contractions, particularly in the lower extremity. Here, we investigated task-dependent differences in lower extremity inhibitory/excitatory (I/E) balance in individuals with stroke and healthy individuals.

Twenty individuals with chronic stroke (age: 62±9 yrs, chronicity: 83±61 mos) and 14 healthy controls (age: 65±9 yrs) performed isolated isometric (ISO) and dynamic (DYN) plantarflexor contractions against a dynamometer. Motor evoked responses (MEPs) were recorded from the paretic medial gastrocnemius (MG) and soleus (SOL). SICI was induced using paired-pulse transcranial magnetic stimulation (TMS) by conditioning the test MEP at 0.7*active motor threshold (aMT) with an interstimulus interval (ISI) of 0.25 ms, while ICF used a conditioning pulse of 0.9*aMT and an ISI of 1.5ms. Test pulses were invoked at stimulator intensity producing an MEP of 1mV peak-to-peak. Inhibitory/excitatory balance was calculated as the ratio of the conditioned MEPs evoked during SICI and ICF, respectively.

I/E balance was similar across the control and stroke groups in the ISO condition for both the MG (p=0.14) and SOL (p=0.40). In the DYN condition, I/E balance in stroke and control groups was similar in MG (p=0.33), but higher in controls than stroke in SOL (p=0.008). I/E balance increased between ISO and DYN conditions in healthy controls in both MG (p=0.03) and SOL (p=0.0008), while in the stroke group, I/E balance increased significantly between ISO and DYN for MG (p=0.004) but not SOL (p=0.06). DYN I/E balance in the MG correlated positively with self-selected walking speed (p=0.006, r=0.43) across both control and stroke groups, and with Dynamic Gait Index score (p=0.02, r=0.44) in the stroke group.

To our knowledge, this is the first reported study of dynamic cortical inhibitory/excitatory balance in the lower extremity. Increased I/E balance during dynamic, relative to isometric, plantarflexion suggests dynamic force production is mediated via disinhibition, rather than facilitation. Associations between I/E balance and gait function, combined with absence of modulation in SOL in the stroke group suggests dynamic I/E balance may be indicative of functional outcomes following stroke.

Disclosures: C.L. Banks: None. V.L. Little: None. Q. Ding: None. C. Patten: None.

Poster

063. Posture and Gait: Aging, Injury, and Disease II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 063.21/MM7

Topic: E.06. Posture and Gait

Support: NSF (Smart and Connected Health) #1502242

Title: Frequency domain measures of motor symptoms in Parkinson's disease

Authors: *E. WADE¹, N. NAGHAVI²

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging and results from a progressive loss of dopaminergic neurons. PD motor features leading to the loss of balance and increased fall risk include slowness of movement, hastening of the gait, blocked movement, paucity of spontaneous movements, reduced arm swing, poor postural stability, and freezing of gait (FOG). Some individuals with PD can overcome FOG with external auditory or visual stimuli. An automated system capable of delivering such cues in ambient settings, where FOG often occurs, requires an accurate algorithm to detect and quantify PD dysfunction. The current study focuses on the development of an algorithm to measure the severity of PD motor symptoms including asymmetry, slowing, and FOG using signals received from wearable inertial sensors (IMUs) attached to the lumbar back, shanks and wrists. The experiment utilizes real-world stimuli to trigger PD symptoms. We will compare motor performances of five individuals with PD to those of five age-matched control participants. We hypothesize that frequency-domain features extracted from IMU measurements will be sensitive to arm swing asymmetry and freezing of gait in PD participants when compared with the control participants. Our prior results indicate the ratio of the acceleration signal power from IMUs on the left and right wrists discriminates between more and less affected sides of the PD participant. In this study we will use these features as well as wavelet features, sample entropy and dimensionless jerk to design an algorithm, using machine learning techniques, to detect occurrence of symptoms in sliding windows of recorded signals during daily activities. Five participants with PD and five age-matched control subjects will be recruited to perform a series of walking, turning and stopping tasks in a 9.1×1.3 m wide with various obstacles. The study uses two-way design with one level of object (0, 1, and 3 objects) and two levels of walkway width (150% or 100% of shoulder width). Participants will repeat each trial 4 laps (20 total laps). At one end, the participants are asked to stop for 3 seconds and then make a turn in a 3×3 ft box marked on the floor and then stop for 3 seconds; at the other end, they are asked to make a narrow turn in a 2×2 ft box with no prior stop. Participants will also make unanticipated stops. Gait events will be classified as walking (approaching and passing the objects), turning (wide

and narrow), stop (expected and unexpected) and gait transition (initiation and termination), and the performance of the algorithm will be compared during these gait events.

Disclosures: E. Wade: None. N. Naghavi: None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.01/MM8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant 145490
MnDRIVE Fellowship

Title: Low intensity ultrasound reversibly inhibits single neuron firing in a tractable invertebrate model

Authors: *M. NEWHOFF¹, C. SMITH², E. EBBINI³, K. A. MESCE⁴

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Abstract: Ultrasound neuromodulation is an emerging technology with therapeutic potential for a range of neurological disorders. Unlike current clinically utilized neuromodulation methods, ultrasound has the potential to noninvasively modulate neuronal activity and reach deep brain structures with high spatial specificity. Clinical introduction has been impeded by inconsistencies in the literature, in part, because despite decades of reports of ultrasound-associated modulation, in a wide range of model systems, ambiguity persists regarding the magnitude and direction of ultrasound's effects. Furthermore, questions persist with respect to the contribution of heat to modulation outcomes, as well as the extent to which modulation is directly related to ultrasound application on targeted tissue versus indirect activation via synaptically-connected sensory cells (e.g., auditory hair cells). Here, we have utilized a tractable invertebrate model system, the medicinal leech, to explore the direct mechanical and thermal effects of ultrasound on the firing rates and spike waveforms of single, identified neurons. We found that ultrasound reduces spontaneous firing activity in the near-absence of heat (0.2°C). This effect appears to be direct on the targeted cells as effects persist in the presence of synaptic blockers. Ultrasound did not evoke activity across the parameter range tested (700Hz - 1kHz; 0.1-2MPa), except in the presence of significant heat (>5°C). Heat alone was equally sufficient to increase activity. Thermal inhibition was only observed at the highest temperatures tested (>80°C), and was largely irreversible. Our overarching goal is to examine how ultrasound directly interacts with single neurons and ion

channels in accessible and functioning networks. We hope the results of this work may prove informative with regards to appropriate clinical applications for this promising technology.

Disclosures: M. Newhoff: None. C. Smith: None. E. Ebbini: None. K.A. Mesce: None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.02/MM9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF-IOS:1755283 (DMB)

Title: Neuropeptide-elicited neuronal switching between single and dual network activity

Authors: *S.-R. H. FAHOUM, D. M. BLITZ
Biol., Miami Univ., Oxford, OH

Abstract: Modulatory inputs can trigger neurons to switch their participation between different networks.

However, few systems allow identification of the cellular mechanisms underlying this neuronal switching. The stomatogastric nervous system (STNS) in the crab, *Cancer borealis*, is particularly accessible to such studies due to the small number of identified network and modulatory neurons. The STNS includes the interacting pyloric (filtering; cycle period ~1s) and gastric mill (chewing; cycle period ~10s) networks. The modulatory projection neuron MCN5 increases pyloric frequency, activates gastric bursting in the IC and DG neurons, and causes the pyloric neuron LPG to switch from pyloric only to dual pyloric/gastric network activity (Norris et al 1996 J Neurophys; Blitz et al 2016 SfN Abstr). The neuropeptide G-SIFamide (SIF) is a MCN5 cotransmitter that mimics the MCN5-elicited increase in pyloric frequency and activation of IC and DG gastric bursting (Dickinson et al 2010 SfN Abstr; Blitz et al 2016). Yet, we find that SIF (5×10^{-6} M) only elicited a complete switch in LPG activity from pyloric only to dual pyloric/gastric network activity in 3/10 preparations. At baseline, the LP neuron inhibits LPG (Marder and Bucher 2007 Annu Rev Physiol). MCN5 decreases LP activity, but SIF increases LP activity (Norris et al 1996; Blitz et al 2016). We hypothesize that SIF excitation of LP prevents a complete switch in LPG activity. When SIF did not cause LPG to switch its activity, SIF+LP hyperpolarization (LP OFF) resulted in a switch (n=6/7). When SIF did cause LPG to switch, SIF+LP OFF increased LPG gastric burst duration (LP ON:LP OFF, 6.3:7.8s; 7.9:8.7s; 4.2:13.2s). SIF excitation of LP likely reflects SIF actions when released from a second unidentified modulatory input. Thus, the LP OFF condition replicates MCN5 actions and enables us to examine the cellular mechanisms whereby SIF switches LPG from single to dual network activity. Thus far, inter-network connections are necessary for neuronal switching (Hooper and

Moulins 1990 J Neurophys; Meyrand et al 1994 J Neurosci). However, our preliminary data suggest a role for LPG intrinsic properties. The SIF-elicited LPG gastric bursting was coordinated with IC (n= 8/14) and DG bursting (n=7/13). Yet, eliminating IC (n=3), DG (n=2), or IC+DG (n=2) activity did not eliminate LPG dual network activity. Additionally, brief LPG depolarization reset its gastric bursting (n=2). We aim to further determine how SIF alters LPG activity. Thus far, our data support modulation of intrinsic properties as a novel mechanism in switching from single to dual network activity.

Disclosures: **S.H. Fahoum:** None. **D.M. Blitz:** None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.03/MM10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01-NS029436 (MPN, LL)

NIH Grant R01-DK071801 (LL)

NIH Grant T32-HL007936 (KD)

Title: Post-feeding time point-dependent, hormonal modulation of the crab gastric mill rhythm

Authors: ***M. P. NUSBAUM**¹, A. P. COOK¹, K. DELANEY², M. S. TEMPORAL¹, L. LI³
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Abstract: The ability of microcircuits to generate different activity patterns when influenced by different modulatory inputs is established mostly from studying the separate influence of single such inputs. Here, we examine the impact of parallel modulation using the isolated crab, *Cancer borealis*, stomatogastric nervous system to probe the feeding state-dependent influence of hormones. We apply to the stomatogastric ganglion hemolymph from unfed vs. recently fed crabs to determine (1) their influence on the VCN-triggered gastric mill (chewing) microcircuit and (2) the identity and amounts of the neuropeptides present in each hemolymph using mass spectrometric (MS) approaches. We showed that the VCN-gastric mill rhythm (VCN-GMR) is altered by hemolymph from crabs fed 1 hr prior but not when taken from unfed crabs (Temporal et al, 2015 SfN Abstr). We now show that 15 min post-fed hemolymph does not alter most VCN-GMR parameters (e.g. protraction and retraction duration, # LG neuron spikes/burst, $p > 0.05$, One-way RM-ANOVA, n=8) that changed in 1 hr post-fed hemolymph. The only changed (increased) parameter was the GMR cycle period ($p = 0.04$, n=8, Holm-Sidak Post-Hoc Test). Correlatively, the weight of the food mass in the crab stomach was no different at 0 hr (n=5) and

1 hr (n=8) post-feeding (p=0.73, Holm-Sidak) but was reduced by 40% at 2 hr post-feeding (n=10; p=0.01 vs 0 hr, p=0.002 vs 1 hr). These data suggest that hemolymph hormone composition changes with time after feeding, leading to changes and effectiveness of the GMR. We are testing this hypothesis by refining our MS analyses to optimize determining the neuropeptide composition in fed vs unfed hemolymph and any qualitative and quantitative changes in its composition. Current challenges include many peptides being (a) present near detection limits, (b) differently sensitive to different MS approaches, and (c) masked by other molecules. First, using dimethyl-labeling on fed or unfed hemolymph before pooling them for comparative MS analysis identified few (10) peptides (n=6 replicates, 3 crabs/replicate). We next used a label-free approach and identified 66 peptides from 11 families in unfed hemolymph (n=3 replicates, 3 crabs/replicate), but variability remained high across replicates (12% peptides identified in all 3 replicates; 38% in 2 of 3). We then tested data-independent acquisition (DIA) MS analysis, which is less biased toward higher intensity species than standard data-dependent acquisition (DDA), using label-free samples. DIA identified 50 more peptides/sample than DDA analysis (n=3 replicates). Next steps include improving quantitation accuracy, then applying the method to unfed and fed hemolymph.

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Poster

064. CPG Modulation

Location: SDCC Halls B-H

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Program #/Poster #: 064.04/MM11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01-NS029436
NIH Grant R35-NS097343

Title: State-dependent cotransmitter modulation of rhythmic motor activity by an identified sensory neuron

Authors: *D. J. POWELL¹, E. MARDER¹, M. P. NUSBAUM²

¹Neurosci., Brandeis Univ., Waltham, MA; ²Dept of Neurosci., Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

Abstract: Most modulatory inputs configure distinct versions of the gastric mill (chewing) and pyloric (pumping/filtering of chewed food) rhythms (Nusbaum et al., 2017 Nat Rev Neurosci) in the stomatogastric ganglion (STG) of the crab *Cancer borealis*, but similar gastric mill rhythms result from activating the projection neuron MCN1 and bath applying CabPK peptide (Saideman et al, 2007 J Neurosci). MCN1 neither contains CabPK nor participates in the CabPK-rhythm.

Despite the similarity of these rhythms, the cellular and synaptic mechanisms underlying their rhythm generation are distinct (Rodriguez et al, 2013 J Neurosci). Additionally, these two gastric mill rhythms respond differently to the feedback influence of an identified multi-transmitter (5HT, ACh, AST-A peptide) sensory neuron (GPR neuron). GPR selectively prolongs the MCN1-gastric mill rhythm retraction phase, via 5HT inhibition of the MCN1 axon terminals (DeLong et al, 2009 J Neurophysiol), while it prolongs retraction and shortens the protraction phase of the CabPK-elicited rhythm (Powell et al, 2017 SFN Abstr). We now aim to identify the sites of GPR synaptic action and the GPR cotransmitters used at each site during its influence on the CabPK-gastric mill rhythm, first focusing on a pivotal gastric mill rhythm generator neuron (LG neuron).

Brief (1 s) focal application of 5HT (10^{-5} M, n=4) or AST-A (10^{-4} M, n=4), but not saline, to the STG neuropil during saline superfusion hyperpolarized the LG neuron from V_{rest} (-51 ± 4.7 mV). The LG response to 5HT was briefer (duration: 37.8 ± 6.2 s) but similarly hyperpolarizing (-3.9 ± 1.3 mV) relative to its response to AST-A (145.5 ± 16.2 s; -3.6 ± 1.4 mV). During a series of suprathreshold depolarizing current steps (n=4), the LG firing rate (7.4 ± 1.6 Hz) decreased in response to each modulator (5HT: 2.4 ± 2.8 Hz; AST-A: 1.9 ± 0.9 Hz). 5HT and AST-A continued to influence LG at -100 mV (maintained via TECC), although the responses became depolarizing (n=4). When LG was functionally isolated from the gastric mill circuit by bath applying picrotoxin (PTX: 10^{-5} M; n=3), its response to suprathreshold depolarization increased to 20.9 ± 2.6 Hz. The LG response to focally applied 5HT and AST persisted in PTX, suggesting a direct action on LG. These responses tended to be briefer than in normal saline but again included a decrease in spike frequency (5-HT: 18.8 ± 1.5 s, 7.1 ± 2.5 Hz, n=3; AST-A: 131.2 ± 25.1 s, 0.8 ± 0.03 Hz, n=3). These results support the hypothesis that, unlike its influence during the MCN1-gastric mill rhythm, GPR uses at least two of its three cotransmitters to inhibit the LG neuron. We next aim to determine how these cotransmitters influence the CabPK-gastric mill rhythm.

Disclosures: **D.J. Powell:** None. **E. Marder:** None. **M.P. Nusbaum:** None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.05/MM12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant NS083319

Title: Nonlinear dynamics of synaptic responses amplify the slow frequency power of multimodal neural oscillations

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¹Federated Dept. of Biol. Sci., NJIT & Rutgers U-Newark, Newark, NJ; ²Inst. for Brain and Neurosci. Res. (IBNR), NJIT, Newark, NJ

Abstract: In a variety of systems, neurons produce multimode oscillatory activity in different frequency bands. The extent to which a neuron participates in different rhythms can be measured by spectral analysis. It is unclear, however, to what extent the synaptic readout of multimodal oscillatory neurons reflects the level of participation in different rhythms. We address this question using the lobster *Homarus americanus* stomatogastric ganglion (STG) circuits, the fast pyloric (~1Hz) and the slow gastric mill (~0.1Hz) rhythms. STG neurons express both the rhythmic activity of their main circuit allegiance and, to some degree, that of the other (Bucher et al. 2006). The pyloric dilator (PD) motor neurons produce fast bursts in pyloric time that wax and wane over the course of the slower gastric mill cycle. In muscles innervated by the PD neurons, EJPs are shaped both by short-term synaptic dynamics and by postsynaptic membrane nonlinearities. Responses to each input burst are too fast to cause summation over consecutive bursts, and therefore do not cause low-pass filtering. Nevertheless, spectral analysis shows that the relative power at gastric mill rhythm frequency is greatly amplified in the postsynaptic responses compared to presynaptic input patterns. This effect is not due to low-pass filtering through synaptic depression because, 1) it is largest at a muscle that shows substantial facilitation and 2) the amplification of power at gastric mill frequency is enhanced by priming effects of ectopic spiking. Ectopic spikes generated in the peripheral PD axon in response to dopamine (Bucher et al., 2003) increase the amplitude of subsequent responses to bursts. As the generation of peripheral ectopic spiking itself changes with the gastric mill modulation of pyloric bursting, priming changes over the course of the gastric mill cycle. However, priming by ectopic spiking is balanced by dopamine effects on the postsynaptic muscle responses. Bath application of dopamine onto the muscle reduces the amplification of relative gastric mill power. These findings indicate that, in multimodal oscillations, the expression of one frequency band can be greatly amplified by nonlinear synaptic dynamics.

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Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.06/MM13

Topic: E.07. Rhythmic Motor Pattern Generation

Title: An ensemble modeling approach to identifying ion channel correlations

Authors: K. TIAN, *A. A. PRINZ

Dept. of Biol., Emory Univ., Atlanta, GA

Abstract: Degenerate coding in neural systems refers to the phenomenon that the same function can be achieved through multiple combinations of the underlying structural elements, such as the mapping from multiple codons to the same amino acid in genetic coding. This phenomenon has been observed in multiple systems, ranging from the pyloric circuit in the crab *Cancer borealis* to olfactory discrimination in humans, and is believed to account for the robustness of a neural system against injury and disease.

For example, the pyloric rhythm in the crab *Cancer borealis* is disrupted after blocking descending neuromodulators, a process called deafferentation, but can recover 3-4 days later [1]. Both computational and experimental studies have shown that multiple combinations of the underlying ionic currents can produce the same pyloric rhythm [2-3], but exactly how the perturbed pyloric circuit switches between those combinations is unclear. In this study, we measure degeneracy by quantifying the pairwise ion channel correlations (ICCs) between all the ionic currents in the pyloric circuit.

To systematically identify ICCs, we first combine a multi-objective evolutionary algorithm (NSGA II) with a biophysical model of the pyloric circuit to generate 1008 models whose outputs resemble the observed rhythms both before and 4 days after deafferentation [4-5]. Each model contains 34 parameters and each parameter is the maximum conductance of a membrane or synaptic current. We then apply both Pearson's correlation and mutual information to quantify the linear and nonlinear ICCs, respectively, and find that the only ICC preserved before and after deafferentation is between the fast transient potassium current (IA) and the slow transient calcium current (ICaS). By applying a filtering method to the correlation matrices before and after deafferentation, we show that ICCs are more tightly regulated before deafferentation.

The ensemble modeling approach above enables a systematic examination of ICCs at the circuit level. We can further cluster all the parameters using dimensionality reduction and network analysis to illustrate the change of degenerate parameter sets during pyloric rhythm recovery.

Acknowledgments

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Disclosures: K. Tian: None. A.A. Prinz: None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

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Program #/Poster #: 064.07/MM14

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Multitasking neurons: A single neuron with multiple hierarchical control roles in multiple networks

Authors: *E. S. HILL, W. N. FROST

Cell Biol. and Anat., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: While it is widely acknowledged that neurons can participate in multiple networks underlying different behaviors, within a given network neurons are still considered to play rather specialized roles, serving for example, as sensory, pattern generating, modulatory or motor neurons. Here we present an example of a single interneuron that plays a surprising number of distinct functional roles in one network, while also playing a significant role in another network. First, C2, a member of the escape swim central pattern generator (CPG) in the marine mollusk *Tritonia*, acts as a network switch for swim onset. At rest the dorsal swim interneurons (DSIs), also members of the swim CPG, recruit inhibition onto one another, preventing them from bursting. C2 powerfully blocks this mutual inhibition, releasing the DSIs to burst together in the swim rhythm. Second, C2 uses an exotic synaptic connection to enforce crisp bursting in the DSIs - a dual-component fast excitatory, slow inhibitory monosynaptic connection that effectively holds the DSIs just above resting potential, allowing them to fire while at the same time building up a slow inhibitory conductance that is unleashed the moment C2 stops firing, causing the DSIs to immediately and deeply hyperpolarize at the end of each burst cycle. Third, C2 optimizes the swim network as it gets going via DSI-mediated modulation of C2's monosynaptic connections to the other CPG members and to the swim flexion motor neurons. Fourth, C2 sustains the swim program via modulated positive feedback to the swim command neuron DRI, effectively bootstrapping the motor program to sustain itself after the brief initiating sensory neuron activity has ceased. Fifth, in addition to the above multiple roles in the swim network, we find that C2 acts to launch *Tritonia's* post-swim, cilia-mediated crawling behavior. Intriguingly, it does so in an "off" manner, with the foot cilia powerfully activated following the termination of a C2 spike train. These observations reinforce a growing appreciation of the rich diversity of function that individual neurons can play in networks that produce behavioral motor programs.

Disclosures: E.S. Hill: None. W.N. Frost: None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.08/NN1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: BBSRC (BB/M024946/1)

Title: Understanding a flexible locomotor pattern in *Xenopus* larvae

Authors: *H. ZHANG, S. ANAGIANNI, F. JACQUOT, D. STANSFIELD
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Abstract: Spinal neural circuits that control rhythmic locomotor activity gradually mature during development and gain the ability to produce flexible movements. Although this ability is essential for all animals, including humans, very little is known about how flexible locomotor patterns can be produced. The spinal locomotor network of young *Xenopus* larvae is already able to produce a flexible pattern during fictive swimming with changing frequency and intensity of motor bursts (Zhang et al., 2011). Therefore, in this study we use 3-day old *Xenopus* larvae to investigate the mechanisms underlying the generation of flexible motor patterns. Locomotor output (ventral root activity) and individual spinal neuron firing are recorded simultaneously using in vivo electrophysiological approaches. It has been shown that a slow modulation in motor burst intensity and frequency is dependent on 5-HT released from hindbrain neurons and NMDA receptors in the spinal cord (Reith and Sillar, 1998; Issberner and Sillar, 2007), raising further questions on how motor circuit neurons are involved and whether other neurotransmitters also play a role in generating flexible locomotion. In this study, a hindbrain lesion at the otic level abolished frequency change in ~87% of the larvae, and applying D-serine (250 micromolar) leads to similar frequency change. Although D-serine caused frequency increase could reach 100%, a clear left-right alternating feature remained. At present, we are systematically characterising the frequency and intensity changes of motor bursts, exploring the firing properties of motor circuit neurons during frequency acceleration and testing the roles of different neurotransmitters (e.g. glycine and dopamine) in initiating and modulating the locomotor pattern during fictive swimming. Data obtained from this study will elucidate the functional development of the spinal central pattern generators controlling locomotion and in particular, shed light on the principle of locomotor speed change. [Reith CA, Sillar KT. Eur J Neurosci. 1998; 10: 1329-40. Issberner JP, Sillar KT. Eur J Neurosci. 2007; 26: 2556. Zhang H-Y, et al. Proc Natl Acad Sci U S A. 2011; 108: 11674-9.]

Disclosures: H. Zhang: None. S. Anagianni: None. F. Jacquot: None. D. Stansfield: None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.09/NN2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: BBSRC
RS MacDonald Charitable Trust

Title: Neural-glia communication in the mammalian spinal cord modulates locomotor networks

Authors: *M. J. BROADHEAD, G. B. MILES
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Abstract: Spinal cord central pattern generator (CPG) networks, which control locomotor activity, are subject to considerable modulation from various sources. Glial-neural interactions can modulate the frequency of CPG output in rodents, with glial-derived adenosine thought to modulate the properties and synaptic connections of interneurons within the CPG. However, the nature of neural-glia communication within the spinal cord remains poorly understood. We have used transgenic mice to visualise Ca²⁺ activity in glia (GCAMP6s) as well as modulate glial activity using mice expressing **D**esigner **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs (DREADDs). Combined with electrophysiology and pharmacology, we are able to visualise and modulate glial activity in spinal motor circuits to better understand their role in locomotion and reveal mechanisms of neural-glia signalling. In hemisectioned spinal cords obtained from GFAP-Cre;GCAMP mice, glia display Ca²⁺ responses following pharmacological induction of fictive locomotion (n=4 experiments). Additionally, stimulation of ventral horn interneurons during patch-clamp recordings evokes Ca²⁺ responses from neighbouring glia (n=7 experiments). To manipulate glial activity, excitatory (hM3Dq) and inhibitory (hM4Di) Cre-dependent DREADD mice were crossed with GFAP-Cre animals. Ca²⁺ imaging in tissue from GFAP-Cre;GCAMP6;hM3Dq/hM4Di mice showed that hM3Dq receptor activation elevated intracellular Ca²⁺ in glia while hM4Di inhibited glial responses to glutamate. Ventral root recordings of locomotor bursts in isolated spinal cords demonstrated that DREADD-based excitation of glia reduced the frequency of locomotion (n=9) while inhibition of glia increased burst frequency (n=11). To address which transmitter or transmitters may be responsible for neural-glia communication, we locally applied various neurotransmitter receptor agonists and recorded Ca²⁺ activity from glia in spinal slices. We find that glia are capable of responding to a range of transmitters, including metabotropic glutamate receptor (mGluR) agonists, GABA and dopamine (n=>2 experiments for each drug). Glia responded most robustly to glutamatergic signalling, supporting a key role for mGluRs in neural-glia communication within the locomotor CPG. In summary, we show that spinal cord glia are active modulators of the locomotor CPG.

We suggest metabotropic glutamatergic signalling as the most likely mechanism of neural-glia communication, allowing activity-dependent feedback control of locomotor circuits.

Disclosures: M.J. Broadhead: None. G.B. Miles: None.

Poster

064. CPG Modulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 064.10/NN3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: BBSRC EastBio Doctoral Training Grant

Title: Dopaminergic modulation of the exploratory headsweep motor program in *Drosophila melanogaster* larvae

Authors: *J. MACLEOD¹, W. LI², S. R. PULVER³

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Abstract: *Drosophila* larvae navigate by moving along chemical, light and temperature gradients. This is achieved by alternating between straight runs and exploratory headsweeps whereby the animal moves its head and olfactory organs left and right before reorienting to direct subsequent runs up or down sensory gradients (Luo et al., 2010). Previous work suggests that exploratory headsweeps may be produced by a dedicated central oscillator that is subject to modulation (Wystrach et al., 2016). Here, we explore how the biogenic amine dopamine influences the production of headsweep motor patterns.

We used the GAL4-UAS system to express the red shifted Channelrhodopsin csChrimson in cells containing Tyrosine Hydroxylase (TH), the rate limiting enzyme in dopamine biosynthesis. Optogenetic stimulation of TH expressing cells *in vivo* strongly inhibited headsweep behaviour in all animals tested. In isolated central nervous system preparations, optogenetic activation of dopaminergic neurons again inhibited fictive headsweeps, while optogenetic inhibition with the blue shifted anion channelrhodopsin GtACR2 triggered fictive headsweeps. Furthermore, in isolated preparations, pharmacologically increasing dopamine levels via bath application of dopamine or the dopamine precursor l-dopa was sufficient to inhibit fictive headsweeps. To attempt to uncover neurons that may underlie the phenotype, electrophysiological recordings of nerve root activity were carried out while imaging calcium dynamics in TH neurons using the genetically encoded calcium indicator GCAMP6f. A high proportion of TH expressing cells in the brain, SEZ and VNC showed rhythmic activity that was correlated with fictive behaviours, including a set of TH expressing neurons in the SEZ whose activity increased when the animal fictively turned in the direction contralateral to the neuron's location.

These data suggest a role for dopamine in the modulation of the headsweep motor pattern and lends support to the notion this behaviour is produced by a dedicated central oscillator subject to modulation. Taken together, these data suggest a previously unknown role of dopaminergic signalling in the production of directed movement.

Luo, L. *et al.* Navigational Decision Making in *Drosophila* Thermotaxis. *J. Neurosci.* **30**, 4261-4272 (2010).

Wystrach, A., Lagogiannis, K. & Webb, B. Continuous lateral oscillations as a core mechanism for taxis in *Drosophila* larvae. *Elife* **5**, (2016).

Disclosures: J. Macleod: None. W. Li: None. S.R. Pulver: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.01/NN4

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CONACYT Grant 59873
CONACYT Grant 219707
NIH grant NS45248

Title: Activation of D₂-like receptors depresses synaptic transmission in deep dorsal horn interneurons and DRPs produced by stimulation of low-threshold afferent fibers

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²Pharmacobiology, CINVESTAV-IPN (sede Sur), Mexico, Mexico; ³Dept Physiol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: It has been shown that dopamine (DA) depresses low-threshold afferent stimulation-evoked primary afferent depolarization (PAD) with no effect on afferent synaptic transmission. These effects are mediated by the activation of D₂, D₃ and probably D₄ receptor subtypes in the *in vitro* mouse spinal cord (SFN Abstracts 422.04/Q5, 2015; 232.02/EE29, 2017). In the present work we further examine the actions of DA and the D₂-like receptor agonist, *quinpirole*, on afferent synaptic transmission in deep dorsal horn interneurons along with effects on PAD. Experiments were carried out on P6 sagittally-hemisected mouse spinal cord with dorsal roots and peripheral nerves attached for afferent stimulation. Stimulus strength was based on multiples of threshold (xT) of the most excitable fibers recorded from the incoming afferent volley, with strengths ≤ 2 xT recruiting only myelinated afferents. PAD was inferred from dorsal root potentials (DRPs) recorded at L₃-L₄ dorsal roots, whereas monosynaptic component of excitatory

postsynaptic currents (EPSCs) or excitatory postsynaptic potentials (EPSPs) were recorded from deep dorsal horn interneurons with micropipettes filled with potassium gluconate containing QX314. We found that the endogenous ligand DA (10 μ M) depressed EPSPs and EPSCs to 67.1 \pm 6.0% (n=17) and 61.9 \pm 7.4% (n=17) of control, respectively. Whereas the D₂-like receptor agonist, *quinpirole* (1 μ M), depressed EPSPs and EPSCs to 64.2 \pm 8.8% (n=10) and 59.4 \pm 8.0% (n=10) of control, respectively. These results were correlated with depression of DRPs by DA (44.2 \pm 2.9%, n=17) and *quinpirole* (53.8 \pm 5.4%, n=10). When the monosynaptic components were isolated with *mephensin* (1 mM), DA depressed EPSPs, EPSCs and DRPs to 49.37 \pm 7.71% (n=4), 42.87 \pm 10.13% (n=4) and 34.82 \pm 5.05% (n=4) of control, respectively. These results suggest that depression of monosynaptic transmission by DA occurs at a postsynaptic level and support the hypothesis that the modulating inhibitory effects by DA on PAD take place at the interneuronal level by the activation of D₂-like receptors (D₂, D₃ and probably D₄ receptor subtypes, as shown previously). We are exploring the effect of the D₂-like agonist, *quinpirole*, on the isolated monosynaptic component of afferent-evoked responses from deep dorsal horn interneurons and on their membrane properties.

Disclosures: J.J. Milla Cruz: None. J.R. Calvo: None. C.M. Villalon: None. S. Hochman: None. J.N. Quevedo: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.02/NN5

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Chewing differentially influences upper limb motor patterns

Authors: *B. SAMULSKI, J. PREBOR, C. ARMITANO, S. MORRISON
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Abstract: The majority of research studies assessing dual-tasking has focused on the effect of performing a cognitive task concurrently with a motor task. Under these conditions the performance of one task often suffers relative to the other, which is referred to as dual-task interference. However, less is known about what residual effects emerge when performing two motor tasks simultaneously. One suggestion is that tasks of a similar nature (i.e. discrete or continuous) may be preferentially coupled due to shared common movement characteristics, such as timing or frequency. When tasks are inherently different, performance will be adversely affected. For example, performing a continuous task should lead to greater decrements in the output of a discrete task at the same time. The purpose of this study was to examine the effects of chewing, a rhythmic continuous task, on the concurrent performance of finger tapping (a continuous action) and simple reaction time (a discrete action) in two age groups. Fifteen young

(20-40 years of age) and fifteen healthy older adults (over 60 years of age) participated in this study. Individuals were asked to chew gum at preferred, slow and fast speeds while simultaneously performing a discrete (simple reaction time) or continuous (finger tapping) motor task. Upper extremity reaction time was recorded by depressing a mouse button with an associated timing mechanism. Tapping was assessed using an accelerometer affixed to a table. Individuals tapped at a preferred and maximal rate. Surface electromyography of the masseter was used to record fast (2Hz), slow (1Hz), and preferred chewing rates. Fast and slow chewing rates were set using an auditory metronome which was switched off during recording. The tapping speed aligned harmonically with the chewing speed when the two were performed together. Reaction times lengthened, meaning responses were slower, when performed in conjunction with chewing. Overall, the results support the dual-task interference theory when performing a discrete motor task with a concurrent continuous motor task. However, a coupling effect was noted when two continuous motor tasks were performed together. Preferred performance frequencies of the tasks vary individually, but converge when performed together. 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.

Disclosures: **B. Samulski:** None. **J. Prebor:** None. **C. Armitano:** None. **S. Morrison:** None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.03/NN6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH (NIDCR) R01-DE023816

Title: Rhythmic movements evoked by both long-train and short-train intracortical microstimulation in primate orofacial sensorimotor cortex

Authors: ***J. D. LAURENCE-CHASEN**, K. TAKAHASHI, C. P. ORSBON, C. F. ROSS, N. G. HATSOPOULOS

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Abstract: Intracortical microstimulation (ICMS) in the orofacial region of sensorimotor cortex evokes a variety of jaw and hyolingual movements. Previous studies have shown that short-train, high frequency (ST) stimulation elicits twitches, whereas long-train, low frequency (LT) stimulation evokes both twitches and complex, sometimes rhythmic movements. However, cortically-evoked tongue and jaw motions are difficult to visualize with standard light cameras. Thus, the goal of this study was to leverage a novel 3D motion capture technique to characterize

and compare the kinematics of ST and LT ICMS-evoked intraoral movements in a non-human primate (*Macaca mulatta*, N=2, both female). In each individual, ICMS was delivered through three multi-electrode arrays located in the orofacial primary motor (M1) and somatosensory (S1) cortices, and the cortical masticatory area (CMA). ST stimulation involved five consecutive 35 ms trains of 0.2 ms duration pulses at 333 Hz with an intertrain duration of 2 s. LT stimulation involved a single 4 s train of 0.2 ms duration pulses at 50 Hz. Simultaneously recorded biplanar x-ray video, processed with X-ray Reconstruction of Moving Morphology (XROMM), allowed us to visualize and quantify jaw and tongue movements. Consistent with previous work, we found that ST ICMS in M1, S1, and CMA frequently elicited twitch-like motions of the jaw or tongue. In contrast, the movements evoked by LT ICMS often involved multiple elements and were rhythmic. Strikingly, we also found that ST ICMS occasionally evoked rhythmic motions in CMA. This result contradicts previous studies that found ST ICMS insufficient for eliciting rhythmic jaw and tongue motions. Methodological differences (i.e. chronic arrays vs. a single penetrating electrode) may explain this discrepancy. Our data suggest that the XROMM workflow can capture and clarify the kinematics of ICMS-evoked movements of intraoral structure. Furthermore, the fact that ST ICMS in CMA evokes rhythmic movements suggests that this cortical area may easily and strongly influence rhythmic movement centers in subcortical areas.

Disclosures: J.D. Laurence-Chasen: None. K. Takahashi: None. C.P. Orsbon: None. C.F. Ross: None. N.G. Hatsopoulos: F. Consulting Fees (e.g., advisory boards); NGH serves as a consultant for Blackrock Microsystems, Inc., the company that provided the micro-electrode arrays for this study..

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.04/NN7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS085387

Title: Convergence of sensory and reticulospinal inputs to glutamatergic commissural interneurons in the lumbar spinal cord

Authors: *A. GIORGI, M.-C. PERREAULT
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Abstract: Sensory inputs help centrally generated motor programs adapt to the changing demands of the external environment. This likely occurs, at least in part, through the convergence of sensory inputs and descending motor commands at the level of the spinal cord.

Here, using single-cell optical recording, we seek to determine if sensory inputs and reticulospinal inputs converge on excitatory descending commissural interneurons (dCINs). We optically recorded calcium responses in glutamatergic dCINs of the L2 segment in brain stem-spinal cord preparations isolated from neonatal vGluT2-Cre/GCaMPx mice that expressed the calcium indicator GCaMP3 or GCaMP6f in VGLUT2 positive neurons. We electrically stimulated the L2 dorsal root (DR) to activate sensory inputs, and the medial and lateral regions of the medullary reticular formation (mMRF and lMRF) to activate two different sources of reticulospinal inputs. Stimulation was expressed in multiples of the current threshold (T) for activation of VGLUT2 dCINs.

Convergence was assessed by concurrent, sub-threshold (0.9T) stimulation of the DR and either the mMRF or the lMRF. Sub-threshold intensity was selected to avoid saturation in the recruitment of VGLUT2 dCINs, which occasionally occurred with DR stimulation at 1T. We found that pairing DR with mMRF recruited 19% of the VGLUT2 dCINs whereas pairing DR with lMRF recruited as much as 81% (n=18 animals, 86 VGLUT2 dCINs). While these results strongly suggest convergence of sensory inputs and reticulospinal inputs on excitatory dCINs, they also indicate differential convergence between sensory inputs and reticulospinal inputs originating in the mMRF and the lMRF.

An important implication of these results is that, in conditions of diminished or weakened descending reticulospinal inputs (e.g., after brain or spinal cord injury), the VGLUT2 dCINs that are normally responsive to these inputs could still be recruited by sensory afferents to participate in functional motor recovery.

Disclosures: A. Giorgi: None. M. Perreault: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.05/NN8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant F31-DC015701-01A1
NIH Grant U19-NS104655-01

Title: Descending control of heading direction and speed during walking in *Drosophila*: A bottleneck at the sensory-motor interface

Authors: *A. RAYSHUBSKIY¹, R. I. WILSON²

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Abstract: What signals does the brain send to the spinal cord? These signals are not simply “motor commands”, given that some upper motor neuron activity correlates with not only

specific movements, but also the passive observation of those same movements performed by another individual (Vigneswaran et al. 2013 Curr Biol).

In this study, we investigated this question in *Drosophila*, an organism where many of the neurons that project from the brain to the ventral nerve cord are individually identifiable and can be targeted for in vivo patch clamp recording. Specifically, we investigated the relationship between walking behavior and descending neuron (DN) activity in flies walking on a spherical treadmill. Anatomical data indicate that walking is likely controlled by several dozen DNs (Namiki et al. 2017 biorXiv). We chose to focus on two DNs in this group (a01 and a02); each of these cells has dendrites in the lateral accessory lobe (LAL) and also several other brain regions that receive multimodal sensory input. The LAL is interesting because it is reciprocally connected with the central complex, which thought to be analogous to the basal ganglia. Thus, the LAL may be analogous to the pre-motor targets of the basal ganglia.

We found that activity in these DNs preceded and predicted spontaneous changes in translational velocity and heading direction. Single neurons were weakly predictive of motor variables, while neural ensembles were more strongly predictive. The difference in the firing rates of left-right copies of the same cell was particularly predictive of turning. Consistent with this result, we found that optogenetically activating single DNs created a transient increase in turning. When turning was evoked by sensory stimuli of various modalities, we found that the relationship between DN activity and turning was similar to what we found for spontaneous turning. During epochs when the fly spontaneously transitioned to motionless resting, these cells were hyperpolarized and their spike rates decreased. Interestingly, DNs still responded to sensory stimuli during these epochs, and they still encoded the laterality of sensory stimuli.

These results, together with anatomical data, imply that these cells integrate multimodal sensory cues. These cells represent stimulus-evoked action biases even in instances where no action actually occurs. Nonetheless, they are not purely “sensory”: they participate in internally-generated actions that occur in the absence of a sensory stimulus, and they closely track spontaneous transitions in overall behavioral state.

Disclosures: R.I. Wilson: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.06/NN9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R01 NS095366

Wings for Life

Title: Postsynaptic response patterns to stimulation of low-threshold hindlimb afferents in flexor- and extensor-aligned rhythm-generating neurons

Authors: *E. Z. LI, D. L. GARCIA-RAMIREZ, L. YAO, K. J. DOUGHERTY
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Abstract: The basic hindlimb locomotor pattern is generated in the thoracolumbar spinal cord by neural circuits known as central pattern generators (CPGs). The locomotor CPG integrates descending commands and ascending sensory information to activate, modulate and halt the rhythmic program. In spinal cord injury and stroke, descending control is impaired but afferent pathways to the CPG remain comparatively intact. Thus, understanding the specific structure of CPG afferent processing circuits may have therapeutic relevance for gait recovery in these disease states. Several recently identified genetically-labeled neuronal populations are thought to participate in CPG circuits on the basis of locomotor alterations following ablation or inhibition. The mammalian CPG structure has not been directly tested, but modeling experiments suggest a two-layer architecture in which rhythm-generating (RG) neurons produce the basic motor program and indirectly recruit motoneurons through an intermediate pattern-forming (PF) neuron population. Using intersectional genetics, a subpopulation of RG neurons has been identified that express *Shox2* during development and lack expression of *Chx10*. Hip angle and ankle load strongly regulate stance/swing phase duration and transition, and these effects are predicted to be mediated at the RG level. To directly test this, we developed a lumbar-hemisected isolated spinal cord preparation with preserved peripheral nerves to study RG neuron operation in *Shox2::cre;Rosa26-lsl-tdTomato;Chx10GFP* mice. In this preparation, RG neuron response to activation of functionally-specific afferent pathways can be measured using whole-cell patch clamp of visually identified RG neurons. Drug-evoked fictive locomotion is possible in the preparation and allows further specification of RG neurons to flexor- and extensor-aligned populations. Under this paradigm, we show that *Shox2* flexor- and extensor-aligned neurons display postsynaptic currents following activation of specific hindlimb afferents which are consistent with predictions from experimental and modeling studies. RG neuron behavior during afferent perturbation of ongoing locomotion and phase-specific changes in afferent responses will yield new insights into operation and feedback control of CPG circuits.

Disclosures: E.Z. Li: None. D.L. Garcia-Ramirez: None. L. Yao: None. K.J. Dougherty: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.07/NN10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF- IOS1454904

Title: Reorganization of proprioceptive inputs facilitates locomotor recovery after injury to the CNS

Authors: *K. A. MESCE¹, A. W. BIGELOW², J. G. PUHL²

¹Entomology and Grad Program in Neurosci., Univ. Minnesota, Saint Paul, MN; ²Univ. of Minnesota, St. Paul, MN

Abstract: Descending information from the brain of the medicinal leech (*Hirudo verbana*) is vital for the initiation and intersegmental coordination of body segments during crawling behavior. After coordinating signals are removed *via* nerve cord transection, leeches can swim but not crawl. Remarkably, several weeks after their initial injury, animals recover their ability to crawl with restored crawl-specific intersegmental coordination across all body segments. Our aim has been to identify the cellular mechanisms responsible for crawl recovery despite our knowledge that no descending fibers have reconnected to their original postsynaptic targets. Thus far, we have determined that the segmentally arranged central pattern generators (one per ganglion) retain their former ability to respond to dopamine, which was found to induce fictive crawling behavior in crawl-recovered individuals. Isolated nerve cords obtained from leeches showing full overt crawl recovery; however, failed to show normal fictive crawl-specific intersegmental coordination (100%, n = 12 animals). Furthermore, we established in transected animals that the segmentally-organized crawl oscillators maintained their influence on adjacent anterior and posterior crawl pattern generators, but collectively, could not generate appropriate crawl-specific phase relationships. Concluding that central oscillator-to-oscillator connections alone were insufficient to generate the intersegmental phase delays required for normal crawling, we turned our attention to understanding how identified sensory neurons might substitute for the loss of coordinating information from the brain. After an extensive evaluation of the peripheral nervous system associated with the leech's body wall, we identified a collection of stretch receptors that showed a dramatic reorganization in their projection patterns. Intracellular Neurobiotin fills of the ventral and dorsal stretch receptors, in both recovered and control leeches, have revealed that only in crawl-recovered leeches do we find that the stretch receptors project beyond their home ganglion, innervating adjacent ganglia (and their associated crawl oscillators). Thus these remodeled stretch receptors are prime candidates to serve as intersegmental coordinating elements. How the timing of this remodeling correlates with the timing of crawl recovery and the genesis of intersegmental coordination is currently under investigation.

Disclosures: K.A. Mesce: None. A.W. Bigelow: None. J.G. Puhl: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.08/NN11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFG Grant BE 6245/1-1
Swedish Research Council

Title: Functional heterogeneity of neurons within a midbrain nucleus driving locomotion in adult zebrafish

Authors: *E. M. BERG, A. EL MANIRA
Karolinska Inst., Stockholm, Sweden

Abstract: Animals navigate their environment with great versatility to find food, escape predators, or find mating partners. While the basic rhythmic locomotor pattern can be generated by circuits in the spinal cord, these circuits are driven by descending projections from the brain. How this descending drive is organized is only beginning to be understood. In the zebrafish, neurons of the nucleus of the medial longitudinal fasciculus (nMLF) in the midbrain are the most rostral cells projecting to the spinal cord. In the larvae, the nMLF has been implicated in controlling swimming behavior in various ways, e.g. by providing a general excitatory drive or by governing steering movements. Thus far, however, most of these studies have regarded the nMLF as a uniform entity and have examined its role on swimming behavior using imaging or ablation. Here we have taken a single-neuron approach to assess the functional heterogeneity of nMLF neurons. For this, we have used single or dual patch-clamp recordings from identified nMLF neurons during spontaneous swimming using the ex-vivo adult zebrafish preparation. First, we show that electrical stimulation of the nMLF region induces swimming activity and that nMLF neurons display cell-specific projection profiles along the rostro-caudal level of the spinal cord. Second, we show that nMLF neurons can be subdivided into several subgroups based on their firing properties with individually identified nMLF neurons consistently displaying either a strong spike frequency adaption, tonic firing, or a delayed firing onset with increasing frequency. Finally, we show that nMLF neurons exhibit different activity patterns during spontaneous swimming. While the activity of all neurons was strongly correlated with swimming activity, they show appreciable differences. Some nMLF neurons displayed a rather sustained activity pattern throughout a swimming episode, while in others the activity was tightly linked to the vigor of swimming. These two neuronal types seem to occupy different regions along the medio-lateral aspect of the nMLF. Thus, our results reveal a large degree of heterogeneity in the nMLF that could endow this nucleus with the necessary versatility to control different aspects of swimming behavior.

Disclosures: E.M. Berg: None. A. El Manira: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.09/NN12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NS100928
NS048844
EB012855

Title: Muscle synergies involved in control of locomotion in the cat: Insights from a computational neuromechanical model

Authors: *A. N. KLISHKO¹, S. N. MARKIN², N. A. SHEVTSOVA², M. A. LEMAY³, I. A. RYBAK², B. I. PRILUTSKY¹

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Abstract: It has been suggested that the nervous system controls movements to overcome multiple degrees of freedom by organizing muscles in a smaller number of groups, modules or muscle synergies. Muscles belonging to the same synergy are activated together and produce a specific basic pattern of activity (Cheung et al. 2005). Despite the widely recognized role of the modular organization of the motor control system and neural constraints responsible for forming muscle synergies during locomotion, the underlying neural mechanisms are currently unknown. The goal of this study was to propose a mechanistic explanation for the organization of muscle synergies during locomotion and investigate the roles of the spinal central pattern generator (CPG) and sensory motion-dependent feedback in the formation of these synergies. EMG activity of 12 hindlimb muscles was recorded in 7 cats during level walking. A nonnegative matrix factorization (NNMF) algorithm was used to extract muscle synergies and their time-dependent contribution to each EMG activity pattern. Five muscle synergies were sufficient to explain over 90% of EMG variance. The EMG patterns and locomotor mechanics were reproduced with high accuracy using a comprehensive neuromechanical model of spinal control of locomotion (Markin et al. 2016). Five muscle synergies were also extracted from the simulated muscle activity patterns. These synergies matched the experimental ones. In a modified model that reproduced walking mechanics and lacking motoneurons of two-joint hamstrings (HA) and rectus femoris (RF), the NNMF analysis revealed that only two synergies comprised of all flexors and extensors, respectively, were sufficient to explain accurately the simulated muscle activity patterns. These results together with the previous findings that these

flexor and extensor muscles-motoneurons have similar patterns in cat fictive and real locomotion (Markin et al.2012), suggest that these two synergies are formed primarily by the CPG. Thus, out of five muscle synergies extracted from the experiment and simulated muscle activities, two synergies were activated by the flexor and extensor half-centers of the CPG, respectively. Two other synergies involved mostly the HA and RF muscles; their activity in the model was formed at the pattern formation level of the CPG with a significant contribution of motion-dependent feedback. The last synergy was formed by the CPG extensor half-centers with the participation of feedback. We concluded that both the spinal CPG and the motion-dependent sensory feedback critically involved in forming the muscle synergies during walking.

Disclosures: **A.N. Klishko:** None. **S.N. Markin:** None. **N.A. Shevtsova:** None. **M.A. Lemay:** None. **I.A. Rybak:** None. **B.I. Prilutsky:** None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.10/NN13

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Sensory cortical control of movement

Authors: ***S. K. KARADIMAS**^{1,2}, **K. SATKUNENDRARAJAH**³, **A. LALIBERTE**⁴, **S. GOSGNACH**⁵, **M. FEHLINGS**²

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Abstract: Locomotion requires continual higher order integrated spatiotemporal information, which is processed in the somatosensory cortex. Motor cortex does not participate in the generation of regular walking. Here, we demonstrate that direct corticospinal output from the primary somatosensory cortex interfaces with a neural circuit in the lumbar spinal cord to control locomotion. Specifically, we have identified that the primary somatosensory cortex independently of the motor cortex, brain stem and other supraspinal locomotor centers modulates activity in the rhythmogenic area of the locomotor central pattern generator (CPG) via cervical excitatory cells. Activation of this pathway promotes movement, while inhibition disrupts the ability to maintain locomotion and ultimately terminates movement. Our findings reveal a novel neural control of movement whereby the somatosensory cortex is part of the automated neural system generating moving in the environment .

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Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

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Program #/Poster #: 065.11/DP08/NN14

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSERC Grant 10020499
Dr. Benno Nigg Chair at U Calgary
NSERC CRC

Title: An artificial neural network learns to optimally combine central pattern generator with sensory feedback for bipedal locomotion

Authors: *H. X. RYU, A. D. KUO
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Abstract: Animal locomotion is governed in part by central pattern generator (CPG) circuits that can produce feedforward rhythmic motor patterns, even in isolated preparations without sensory feedback. Locomotion is also governed in part by reflex chains, using sensory feedback to stabilize against external perturbations. Although CPGs and reflexes are each well-characterized independently, they are also understood to act together during normal, intact locomotion. But how these two independent processes work together is not understood. Nor is it known how CPGs might be adaptive, as might be expected if there is neural plasticity. But if an adaptive process can learn to control locomotion, it might also find an operational means to combine feedforward and feedback. Here we propose an artificial neural network (ANN) that learns to control a model of bipedal, dynamic walking. The proposed ANN implicitly learns an internal (feedforward) model of locomotion dynamics to optimally predict the body state, which is corrected with sensory feedback. The resulting estimate is then used to drive state-dependent motor commands for the legs. The ANN can produce fictive locomotion when isolated from feedback, but could also be interpreted as a feedback-driven state estimator. The resulting gait pattern also coincides with a minimum of energetic cost of transport, and exhibits high robustness to perturbations. The model demonstrates that feedback can help counter unexpected perturbations or uneven terrain, and feedforward help counter noisy or imperfect sensors. The combination of the two could thus yield optimal locomotor performance.

Disclosures: H.X. Ryu: None. A.D. Kuo: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

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Program #/Poster #: 065.12/NN15

Topic: E.07. Rhythmic Motor Pattern Generation

Support: MRC/G0400551

BB/H009906/1

BB/K018515/1

BB/K019015/1

BB/P00766X/1

Title: A hunger state dependent central control switch for assessing food value

Authors: *G. KEMENES, K. STARAS, M. CROSSLEY

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Abstract: Hunger state can alter the perceived value of a stimulus, even to the extent that the same sensory cue can trigger opposing behaviours driven by a single neural network. How such perceptual shifts bias motor pattern selection in the nervous system remains enigmatic. Here we challenged food-deprived and sated *Lymnaea* to choose between two mutually exclusive behaviours, ingestion or egestion, produced by the same feeding central pattern generator. Decoding the underlying neural circuit reveals that activity of central dopaminergic interneurons defines hunger state and drives network reconfiguration, biasing sated animals towards the rejection of stimuli deemed palatable by food-deprived animals. We also demonstrate that this perceptual shift occurs in the absence of sensory retuning. Our study reveals a potentially general centralized mechanism by which animals make value-based decisions in a hunger state dependent manner.

Disclosures: G. Kemenes: None. K. Staras: None. M. Crossley: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.13/NN16

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant R01 NS095366
Wings for life

Title: Alterations in spinal cord injury-induced plasticity of spinal rhythm generating interneurons following treadmill training with epidural stimulation in mouse

Authors: ***D. GARCIA-RAMIREZ**¹, N. HA¹, L. YAO¹, K. A. SCHMIDT², S. F. GISZTER¹, K. J. DOUGHERTY¹

¹Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; ²Biomed. Engineering, Sci. and Hlth. Systems, Drexel Univ., Philadelphia, PA

Abstract: Neuronal circuitry generating locomotion is located in the thoracolumbar spinal cord. Spinal rhythm generating interneurons (INs) convert descending inputs into rhythmic outputs. Rhythm generating INs are strongly influenced by afferent feedback and supraspinal control, including serotonergic modulation. Spinal cord injury (SCI) disrupts the descending control of spinal locomotor circuits but this circuitry is located below the level of most SCIs and is relatively intact; however, plasticity occurs. Current clinical therapies to recover motor control after SCI include treadmill training and epidural stimulation (ES), targeting the locomotor circuitry. However, the state of the spinal circuits targeted after SCI and rehabilitation is poorly understood. Rhythm generating INs should be a prime access point for these treatments. Previously we found that rhythm generating INs expressing the transcription factor Shox2 are modulated by serotonin (5-HT) in a dose-dependent manner, producing inhibitory actions at low concentrations and excitatory actions at high concentrations. Further, Shox2 INs received mainly polysynaptic afferent input mediated by both excitatory and inhibitory pathways. After SCI, 5-HT only increased the excitability of Shox2 INs, regardless of concentration, and Shox2 INs received only excitatory inputs from afferent pathways. The main objective of the present study was to identify how the combination of treadmill training and ES then modifies the SCI-induced plastic changes in afferent-evoked inputs to and 5-HT modulation of Shox2 INs. Complete thoracic spinal transections were performed on adult Shox2::Cre;Rosa26-lsl-tdTomato mice. ES wires were implanted at lumbar level L2 for ES during treadmill training (SCI+ES) for 5 weeks after SCI. Whole cell patch clamp recordings targeted Shox2 INs in lumbar spinal slices, with dorsal roots attached for afferent stimulation, from SCI and SCI+ES mice. After treadmill training with ES, 5-HT hyperpolarized Shox2 INs and there was a return of afferent-evoked inhibitory inputs to Shox2 INs. This suggests that treadmill training with ES shifts the balance of excitatory/inhibitory afferent pathways to Shox2 INs and the serotonergic control of Shox2 INs back towards that observed in the uninjured state.

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Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 065.14/OO1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: HHMI

Title: Layered development of V2a descending projection underlying maturation of motor repertoire in larval zebrafish

Authors: A. PUJALA, *M. KOYAMA
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Abstract: Many animals are born with a minimal set of reflexive behaviors but rapidly acquire increasingly complex behaviors after birth. Concurrent with the rapid development of behavior is the equally rapid formation of new connections in the brain. Although the molecular and genetic mechanisms underlying the formation of new connections during development have been extensively studied, little is known of how the brain can integrate new connections for refined behavior while maintaining the functionality of existing reflex circuits. To address this question, we focus on the hindbrain V2a descending neurons that are known to play an important role in locomotion. We examine how their projections to the spinal cord are organized to control two distinct motor patterns that come online at different ages in the larval zebrafish: evoked powerful locomotion that already exists at the time of hatching, and spontaneous weaker locomotion that develops later. Systematic birthdating and calcium imaging analyses of the whole hindbrain V2a descending population reveal that the early-born neurons are recruited during evoked fast locomotion while the late-born neurons are recruited during spontaneous slow locomotion. Furthermore, they form anatomically and functionally distinct spinal projections organized in layers based on the time of differentiation. Detailed electrophysiological and anatomical characterizations of the subset of V2a descending neurons further reveal that each age group forms synaptic connections to distinct spinal neurons with biophysical properties (conduction velocity, synaptic decay constant) suitable for the speed of the motor pattern each contributes. Behavioral analysis after the ablation of each age group shows that each age group indeed contributes to distinct motor patterns; the early-born group contributes to large body bends, such as the ones observed during escape behavior, while the contributions of the late-born group contributes to spontaneous locomotion. Taken together, we uncover parallel descending pathways of hindbrain V2a neurons, organized in layers based on the time of differentiation. These parallel pathways underlie distinct motor patterns that differ in strength and ontogeny. This suggests that such birthtime-related neuropil separation, observed in many brain regions, is

an organizing principle by which nervous systems establish new circuits for more refined behavior without disrupting preexisting circuits.

Disclosures: A. Pujala: None. M. Koyama: None.

Poster

065. Rhythmic Motor Pattern Generation: Afferent and Descending Control

Location: SDCC Halls B-H

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Program #/Poster #: 065.15/OO2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DOD Award # SCI140238
NINDS Grant 1R01 NS089972

Title: Defensive behavior elicited via deep brain stimulation of the midbrain in freely moving micropigs

Authors: *I. OPRIS¹, S. CHANG¹, F. D. BENAVIDES¹, F. J. SANCHEZ¹, L. M. VILLAMIL¹, A. J. SANTAMARIA¹, Y. NUNEZ-GOMEZ², J. P. SOLANO², J. D. GUEST^{1,3}, B. R. NOGA^{1,3}
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Abstract: Objective: Animal and human survival depends on appropriate defensive behavior. Defensive behavior is controlled in part by midbrain circuits, including the mesencephalic locomotor region (MLR) and the periaqueductal grey (PAG). Deep brain stimulation (DBS) of the midbrain of the Yucatan micropig is a promising model for assessing neuromodulation of defensive behavior. However, a quantitative assessment of the MLR/PAG evoked responses via local field potentials (LFPs) and electromyographic (EMG) activity during defensive behavior is lacking.

Methods: DBS of the MLR [cuneiform (CnF) and pedunculopontine (PPN) nuclei] and PAG was applied bilaterally using electrode arrays. LFP and EMG activity were evaluated quantitatively. Patterns of muscle activation in agonist/antagonist muscles of all four limbs were recorded using intramuscular EMG electrodes. EMG signals were rectified and band-pass filtered. Stance and swing phases of each limb during locomotion were characterized with and without stimulation. Circular statistics were used to determine coordination of flexor and extensor activity from EMG recordings.

Results: In general, DBS of the midbrain region of micropigs (n=6) increased the level of alertness. Stimulation of the PAG in open field produced fight or flight responses including freezing, cowering, turning and escape behavior, vocalizations and aggressive movements. CnF stimulation initiated and facilitated ongoing locomotion, increasing the speed as current/frequency increased. Postural effects including loss of extensor tone resulting in the

animal sitting or lying down were observed with stimulation of the PPN. LFP power increased with initiation of movement and with increased speed of locomotion.

Conclusion: These experiments demonstrate that the CnF nucleus initiated locomotion in open field, PPN stimulation caused postural effects and the activation of PAG elicited defensive fight-or-flight behavior. The micropig model and the DBS approach may be very useful to dissect the neuronal circuitry of defensive behaviors including locomotion. This knowledge is critical to the feasibility, safety and tolerability of MLR stimulation for SCI and gait disorders.

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Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.01/OO3

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant DA013185

Title: Optogenetic activation of POMC terminals in the medial preoptic nucleus regulates lordosis behavior

Authors: *C. S. JOHNSON, P. E. MICEVYCH
Neurobio., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Lordosis, the stereotypical behavior of female sexual receptivity, is elicited by estrogen and progesterone signaling in a limbic-hypothalamic circuit, which integrates sensory and hormonal information. Estradiol acts through membrane receptors to rapidly activate a part of this circuit involving the arcuate (ARH), medial preoptic (MPN), and ventromedial nuclei of the hypothalamus. Activation of this sub-circuit is necessary for full lordosis behavior. Previous work has indicated that estradiol-dependent beta-endorphin release in the MPN from ARH pro-opiomelanocortin (POMC) neurons is required for full lordosis behavior. Beta-endorphin release activates mu opioid receptors (MOR), which are rapidly internalized. This internalization results in a transient, but necessary, inhibition of lordosis behavior. To functionally dissect this circuit, we tested the effect of activating POMC axon terminals in the MPN in sexually receptive female mice. Female POMC-Cre mice were ovariectomized and channelrhodopsin 2 was delivered via an adeno-associated vector bilaterally to the ARH, followed by ferrule fiber implantation into the MPN. Mice were primed with estrogen and progesterone prior to behavioral testing for sexual receptivity, which was assessed by measuring the lordosis quotient (number of times a female exhibits lordosis when mounted by a male, divided by total number of mounts). Following an

initial trial for sexual receptivity, blue light was delivered for the duration of the lordosis test. Immunohistochemistry was run to evaluate MOR internalization in the MPN. Our results show that optogenetic activation of POMC terminals in the MPN results in MOR internalization and attenuates lordosis behavior, thus indicating that endogenous opioid inhibition of sexual receptivity requires the ARH POMC input to the MPN.

Disclosures: C.S. Johnson: None. P.E. Micevych: None.

Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.02/OO4

Topic: F.02. Behavioral Neuroendocrinology

Support: RISE GM07163

Title: Membrane G protein-coupled estrogen receptor-1 (GPER) activation in the ARH reduces medial preoptic nucleus μ -opioid receptors activity to facilitate sexual receptivity

Authors: *R. R. TOMINNA¹, S. CHOKR², M. LA FOREST¹, K. SINCHAK¹

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Abstract: In the arcuate nucleus of the hypothalamus (ARH), the activation estrogen receptor- α (ER α) followed approximately 48 hours later by G protein-coupled estrogen receptor-1 (GPER; aka GPR30) activation facilitates sexual receptivity (lordosis) in ovariectomized (OVX) rats. The initial actions of estradiol include priming lordosis circuits and inhibiting lordosis by activating ARH β -endorphin (β -END) neurons that project to the medial preoptic nucleus (MPN). β -END neurotransmission, in turn, activate MPN μ -opioid receptors (MOP) producing inhibition of lordosis. ARH infusion of non-esterified 17 β -estradiol (E2) 47.5 hours after 17 β -estradiol benzoate (2 μ g EB) priming facilitates lordosis rapidly within 30 minutes through the deactivation of MPN MOP. Previous results from our laboratory demonstrated that like E2, the selective estrogen receptor modulators (SERMs), ICI 162,473 (ICI) and tamoxifen (TAM), facilitate lordosis via activation of GPER in EB primed rats that deactivates MPN MOP. Using cell fractionation techniques and western blot we demonstrated that GPER are expressed both in plasma membrane and cytosolic ARH fractions (Feri et al 2016). However, it appears that plasma membrane associated GPER mediates E2 effects. Previously, we showed that membrane impermeable estradiol (17 β -estradiol conjugated to biotin; E-biotin) infused into the ARH of EB primed rats facilitated lordosis within 30 minutes. However, we did not confirm that the E-biotin was reducing β -END neurotransmission. Therefore, we tested the hypothesis that E-biotin rapidly facilitates lordosis via membrane GPER through the orphanin FQ-orphanin receptor-like

receptor-1 (OFQ/N-ORL-1) system and reduces β -END neurotransmission as measured by a reduction in MPN MOP activity. ARH infusion of E-biotin ARH 47.5 hours after EB priming, facilitated lordosis within 30 minutes and significantly reduced MPN MOP activation as measured by MOP immunoreactive intensity staining. Pretreatment of UFP-101, an ORL-1 selective antagonist, or G-15, GPER selective antagonist, blocked the facilitation of lordosis and deactivation of MPN MOP by ARH infusion of E-Biotin. These data indicate that membrane GPER mediates the E2 facilitation of lordosis by activating OFQ/N neurotransmission, which inhibits β -END neurotransmission to reduce MPN MOP activation. Multiple ER pathways are activated sequentially over time to facilitate sexual receptivity. Understanding the location, timing, and type of ER signaling pathway(s) that are activated to regulate reproduction is important for enhancing SERM therapies for women's health.

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Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.03/OO5

Topic: F.02. Behavioral Neuroendocrinology

Title: Dopaminergic regulation of mate competition aggression in male Zebra finches: Effects of prior winning experience and recent aggressive behavior on tyrosine hydroxylase immunoreactivity in the social behavior network

Authors: ***E. J. JACOBSON**¹, **S. C. MOLL**², **A. M. SMITH**², **J. PRIBBLE**², **S. A. HEIMOVICS**³

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Abstract: Goal-directed behaviors, such as aggression, are modulated by transient fluctuations in dopamine (DA). Also, in some species, accumulating winning experience upregulates DA neurotransmission and enhances future competitive ability. In the present study, we used the Zebra finch model system to investigate the effect of prior winning experience during aggressive competition over mates on both future winning ability and dopaminergic regulation of aggressive behavior. Unpaired male dyads were exposed to a female stimulus (or empty cage control) across a wire partition for 15min. Agonistic behaviors during this training experience were quantified, and either the winner of the fight (or a randomly selected individual from control dyads) were placed into a holding cage. Two hours later, subjects underwent a test competition: they were assigned to a novel dyad, presented with a novel female (or empty cage control), and aggressive behavior again quantified for 15min. Immediately after the test, subject brains were collected and processed for

immunohistochemistry for both phosphorylated and total (i.e. phosphorylated and unphosphorylated) tyrosine hydroxylase (pTH and tTH, respectively) as a proxy measure for DA synthesis. While a win during training did not influence competitive ability during the test, relative levels of pTH and tTH within social behavior network (SBN) nuclei were significantly modulated by both winning during training and fighting during the test. Subjects that fought during the test had significantly higher pTH in the medial preoptic nucleus (POM) and bed nucleus of the stria terminalis (BST) than controls. This suggests that DA synthesis in these nuclei acutely regulates mate competition aggression. Notably, relative to controls, subjects that fought during the test also had significantly lower tTH in BST. This suggests that acute TH phosphorylation may deplete the pool of TH protein in a region-specific manner. Fighting during the test also elevated pTH in the ventral tegmental area (VTA), but remarkably, winning during training on its own was also sufficient to elevate pTH in VTA. Further, winning during training significantly reduced tTH in VTA. Taken together, these data suggests long-lasting effects of mate competition aggression on DA synthesis in this nucleus. Finally, winning during training significantly elevated and fighting during the test significantly lowered tTH in the midbrain central gray. In all, these findings are consistent with the established role for DA in aggression, but highlight the interplay between short- and long-term effects of aggressive behavior on dopaminergic neurotransmission.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Program #/Poster #: 066.04/OO6

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF Grant # IOS 1256898

Title: Effect of serotonin on mating success in *teleopsis dalmanni*

Authors: *E. R. SCOTT¹, J. G. SWALLOW¹, K. RENNER²

¹Integrative Biol., Univ. of Colorado Denver, Denver, CO; ²Biol., Univ. of South Dakota, Vermillion, SD

Abstract: Successful mating is one of the most important fitness related behaviors and the primary focus of many behavioral studies. Neuronal mechanisms that mediate whether a pair successfully mates or not are well understood in invertebrates. Invertebrates, such as the dipteran, *Teleopsis dalmanni*, share some of the same conserved neuronal mechanisms as vertebrates. While the monoamines dopamine (DA) and octopamine (OA) have been implicated

in a variety of reproductive behaviors, the role of serotonin (5-HT) has not been fully examined. We hypothesized that, similar to its association with aggressive behavior, 5-HT would be associated with boldness in seeking a mate and thereby increase mating frequency in males but not in females. Female and male *T. dalmanni* were isolated for four days while being fed 5-HTP, a precursor to 5-HT, or control food. Flies were then randomly paired and allowed to interact for 20 minutes in an arena while their behaviors were recorded and scored. High Performance Liquid Chromatography (HPLC) with Electrochemical (ED) was used as a validation method to ensure that 5-HT was elevated. Preliminary results from the pilot study do not support the hypothesis that mating frequency would increase in male *T. dalmanni* with an increased level of global 5-HT. 5-HT was instead found to have no effect on frequency of successful mating events, but rather showed a trend to decrease the number of attempts made by males.

Disclosures: E.R. Scott: None. J.G. Swallow: None. K. Renner: None.

Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.05/OO7

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF Grant IOS 1256898

Title: Mating-receptivity in female dipterans is mediated by daily fluctuations of dopamine levels

Authors: *E. J. SANDERS¹, A. N. BUBAK², K. J. RENNER³, J. G. SWALLOW¹

¹Dept. of Integrative Biol., Univ. of Colorado Denver, Denver, CO; ²Dept. of Neurol., Univ. of Colorado Denver - Anschutz Med. Campus, Aurora, CO; ³Dept. of Biol., Univ. of South Dakota, Vermillion, SD

Abstract: Dipterans, like vertebrates, are subject to circadian rhythms. Circadian rhythms can cause physiological changes that lead to differences in behavioral responses throughout the day. These physiological changes include fluctuations in monoamine levels, such as dopamine and serotonin. Invertebrates, for example, stalk-eyed flies (*Teleopsis dalmanni*), are a useful model for studying the function of conserved mechanisms, like monoamines, that are also seen in vertebrates. We designed a circadian rhythm study in which flies were sacrificed every four hours and used HPLC with electrochemical detection (ED) to detect changes in in whole-brain levels of dopamine, serotonin, and octopamine throughout the day. Octopamine and serotonin stayed relatively level throughout the day in both males and females. Female stalk-eyed flies were found to have a spike in dopamine levels from 5 to 7 pm, which is when the flies tend to roost, while male levels stayed stable. This spike was not seen at other times throughout the day.

We hypothesized that this spike in dopamine would lead to increased mating receptivity in females. To test this, we administered 3-Iodo-L-tyrosine 97% (3-IY), which inhibits the enzyme Tyrosine Hydroxylase and decreases the synthesis of L-Dopa, to knock down dopamine globally in female flies. Both control and treated females were isolated from males, who were also isolated from other females, for three days while the drug was being administered. Then mating receptivity was assessed by placing each female one-on-one with a male in an arena. Their mating behaviors were recorded and scored. HPLC with ED and Immunohistochemistry were used as validation methods to ensure that dopamine was knocked down. The results supported the hypothesis that a circadian increase in dopamine plays a significant role in mating receptivity in female stalk-eyed flies.

Disclosures: **E.J. Sanders:** None. **A.N. Bubak:** None. **K.J. Renner:** None. **J.G. Swallow:** None.

Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.06/OO8

Topic: F.02. Behavioral Neuroendocrinology

Title: Measuring fecal corticosterone in male prairie voles

Authors: ***S. MCGLOTHLIN**¹, **J. CURTIS**²

¹Oklahoma State Univ. Ctr. for Hlth. Scienc, Tulsa, OK; ²Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK

Abstract: Prairie voles are highly social animals capable of forming monogamous bonds between males and females. Stress can impact the development of a monogamous “pair-bond” in this species. Interestingly, the effects of stress on pair-bond formation are sexually dimorphic: stress increases the likelihood of a pair bond in males, but decreases it in females. We are using a female mate choice test to determine whether stress in males can affect mate selection by females. Fecal corticosterone levels are being used to monitor stress responses, as this approach is less invasive and allows for repeated measurements from the same individual, reducing animal usage. We are examining several stress paradigms to see which has the greatest effect on fecal corticosterone levels. For example, we have tested the effect of 48 hours of social isolation on fecal corticosterone in males, as isolation is known to be a stressor in this species. The results then were compared to those from plasma samples collected from the same animals. We found no statistically significant effect of 48 hours of isolation stress on either fecal or plasma corticosterone levels in male prairie voles. Examination of other stress paradigms such as exposure to a more aggressive same-sex conspecific are on-going.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

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NIMHD Grant 5G12MD007592

Title: The roles of estrogen receptor alpha and beta in sexual behavior and social preferences in female prairie voles

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Abstract: Estrogen acting via estrogen receptor (ER), α and β , play a critical role in regulating sociosexual behavior. However, the specific role, interaction, or antagonistic function of these two receptors in regulating social versus sexual behavior is unclear. Prairie voles (*Microtus ochragaster*) are an excellent model system to try and understand the role/interaction, synergistic or agonistic, of these receptors in regulating female sociosexual behavior. Female prairie voles require prolonged male exposure for estrus, which is associated with increasing 17 β -estradiol (E2). Exogenous E2 facilitates the formation of selective social attachments in female prairie voles, which may be contingent on mating. It remains unclear whether E2 contributes to partner preferences independently from mating and whether ER α and/or ER β is involved. We hypothesized that ER β activation contributes to pair bonding, whereas ER α activation mediates sexual receptivity in the socially monogamous female prairie vole. To test this hypothesis, adult females received one of the following treatments via injection for three days: vehicle (hydroxypropyl- β -cyclodextrin), ER α agonist (PPT, 5mg/kg), ER β agonist (DPN, 5mg/kg), or non-selective ER agonist (E2, 5mg/kg). 24 hours following the last treatment, females were paired with a sexually-experienced male for a 6-hour cohabitation scored for mating. Immediately following cohabitation, a 3-hour social preference test was conducted in which female subjects could freely interact with the familiar partner and a novel male. Durations of huddling with each stimulus were used to determine preferences. Brains and uteri were collected after the preference test (the former as a proxy for peripheral ER α activation). E2 treatment significantly increased mating and uterine weight in females, whereas sexual receptivity was low or absent in all other treatment groups. PPT-treated females were the only other group displaying uterine hypertrophy. VEH- and DPN-treated females displayed significant partner preference, whereas E2- and PPT-treated females failed to display a partner preference. Contrary to our

hypothesis, but consistent with studies in male voles, these data suggest that ER α activation suppressed the formation of selective attachments. ER α activation alone failed to support sexual receptivity despite increased uterine hypertrophy, indicating the involvement of an additional estrogen receptor and/or mechanism in prairie voles, unlike other rodents. Neurochemicals implicated in vole sociosexual behavior will be visualized in brain tissue to identify potential mechanisms for these effects of ER activation on behavior.

Disclosures: **D. Torres:** None. **J.M. Landeros:** None. **A.N. Perry:** None. **B.S. Cushing:** None.

Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.08/OO10

Topic: F.02. Behavioral Neuroendocrinology

Title: Does female mate choice influence monogamous pair bond formation and reproduction in prairie voles?

Authors: ***A. FRANCIS**¹, J. T. CURTIS²

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Abstract: The prairie vole model is well established for the study of social bonds, particularly monogamous pair bonds between mated pairs. Social bonds are known to increase reproductive success by allowing for additional care of offspring and providing some protection against predators. Previous studies in our lab have shown that male prairie voles are more likely to maintain monogamous pair bonds in pairings that result in a short latency to pregnancy. The objective of this study was to determine whether female mate choice influences the latency to pregnancy, and thus the affiliative behavior of prairie voles.

Sexually naïve female prairie voles were allowed to choose between two males, then were paired either with the male of choice, the non-preferred male, or a randomly selected male. Two weeks after pairing, either the female or male from a given pair were subjected to a partner preference test. Affiliative behavior from the partner preference test were combined with latency to the birth of a first litter of pups for each group and each sex to assess whether mate choice decreases the latency to pregnancy of a pairing as well as the expression of a successful pair bond. Since vole pairings typically are made randomly in the laboratory and do not allow for any sort of mate choice by the subjects, the results of this experiment may help to inform future experimental design.

Disclosures: **A. Francis:** None. **J.T. Curtis:** None.

Poster

066. Neuroendocrinology of Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH 2R25GM049011

NIH 5G12MD007592

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Latino Alcohol and Health Disparities Research Center

Title: The effects of alcohol on prosocial behavior in the prairie vole

Authors: *R. GRINCEVICIUTE¹, Q. W. VIDAL², R. J. ORTIZ², K. R. HERNANDEZ¹, A. N. PERRY³, C. A. FIELD⁴, B. S. CUSHING²

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Abstract: Alcohol consumption is highly prevalent and deeply embedded in most cultures. However, alcohol use disorder can affect social behavior and can be associated with heightened aggression, intimate partner violence and changes in parenting styles. Prairie voles (*Microtus ochrogaster*) are socially monogamous rodents that display pair-bonding and biparental care. Previous studies demonstrated that prairie voles readily drink alcohol and like humans they respond similarly to stress and social encounters as well as the rewarding effects of alcohol. These characteristics make them a human-relevant model system for studying social behavior, well-suited studying the effects of voluntary alcohol consumption on social behaviors. The objective of our research was to examine the effects of alcohol consumption on adult relationships and parental care. We hypothesized that drinking alcohol would disrupt prosocial behavior in both males and females. To test this hypothesis, adult females and males (PD >60) were paired and allowed to produce 4 litters. The initial breeding pairs were placed into two groups: alcohol and water-only controls. The alcohol group had 24-hour access to 10% ethanol and water while the water group only had access to water. Ethanol was removed and replaced with water after the weaning of the first litter in order to examine long-term recovery in the alcohol group. The mating latency and affiliation were examined during the initial 72-hour cohabitation. Parental care tests were conducted after the birth of each litter and partner preference tests were conducted 7 days after the birth of the 4th litter to evaluate pair bond maintenance and stability. We found that alcohol pairs consumed approximately 9.9 mL (19 g/kg) alcohol per day, which remained relatively stable over the entire course of the study. Initial mating behavior and parental care were unaffected by alcohol consumption. However, there were some subtle effects of experience and sex differences on certain aspects of parental care.

Additionally, males and females in both treatment groups displayed robust social preferences for their familiar partner and aggression selectively towards the stranger. However, subjects with a history of alcohol consumption displayed sex-specific alterations in the amount of time spent with the novel individual, with alcohol females spending more and alcohol males spending less time with the stranger. These data suggest that a history of moderate alcohol consumption has subtle lingering effects on prosocial behavior but is not associated with pair bond dissolution. Also reported are the effects of prior alcohol consumption on hypothalamic oxytocin expression.

Disclosures: **R. Grinceviciute:** None. **Q.W. Vidal:** None. **R.J. Ortiz:** None. **K.R. Hernandez:** None. **A.N. Perry:** None. **C.A. Field:** None. **B.S. Cushing:** None.

Poster

066. Neuroendocrinology of Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 2R25GM069621-14
NIH Grant 5G12MD007592-25
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Title: Population differences in the neural microarchitecture of the prairie vole brain within regions relevant to emotionality and prosocial behavior

Authors: ***R. J. ORTIZ**¹, J. R. YEE², P. P. KULKARNI³, A. N. PERRY¹, I. E. KEHOE³, B. KEANE⁴, N. G. SOLOMON⁴, C. FERRIS², B. S. CUSHING¹

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Abstract: Culture and upbringing influence an individual's emotional and behavioral traits. Prairie voles (*Microtus ochrogaster*) are socially monogamous rodents that provide an excellent animal model system for studying the impact of early life environment on emotionality and behavior. Voles originating from different geographical regions, Kansas (KS) and Illinois (IL), display significant differences in levels of prosocial behavior, as KS voles are less alloparental and affiliative compared to IL voles, and these trait differences are maintained under standard housing conditions and transmitted from parent to offspring in cross-fostering studies. Maternal influences are particularly important in shaping offspring phenotypes, as the male offspring of KS dams and IL sires (KI males) display an exaggerated KS phenotype. KS and IL males also display differences in the expression of estrogen receptors, vasopressin, and oxytocin, which contribute to their different patterns of prosocial behavior. However, it is likely that additional

brain regions and different connection profiles directly contribute to their overall emotionality and temperament, which would, in turn, influence their expression of prosocial behavior. We hypothesized that the microarchitecture of areas associated with aggression, vigilance, and arousal is different in KI and IL males. Diffusion-Weighted imaging (DWI) was performed to analyze differences in anisotropy of water molecules crossing grey matter between KI and IL males (n=8 per group, 115 areas). KI males showed significantly more developed tracts in areas mediating emotional expression and aggression (olfactory tubercles, prelimbic cortex, anterior hypothalamus, paraventricular nucleus of the hypothalamus and amygdala; $p < 0.05$ for all). Additionally, KI males showed significantly more developed connections in areas associated with vigilance and arousal (dorsal nucleus raphe, nucleus raphe magnus, paraflocculus, red nucleus, tegmental reticular nucleus, and vestibular nuclei; $p < 0.05$ for all). These results support the hypothesis that KI and IL males have differences in the microarchitecture of brain regions regulating emotionality, vigilance, and arousal. Furthermore, they provide a framework for understanding how individual differences in brain microarchitecture can influence emotionality and temperament and ultimately impact the expression of prosocial behavior. Resting-state connectivity and neural response to predator odor (BOLD) are currently being analyzed to further characterize functional differences in the brains of KI and IL males.

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Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.11/OO13

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 5612MD007592
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Title: The effects of cohabitation and reproductive activation on microglia in male and female prairie voles

Authors: A. ENRIQUEZ, *A. N. PERRY, B. S. CUSHING
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Abstract: Prairie voles are socially monogamous rodents that form long-term pair bonds. Exposure to a novel member of the opposite sex stimulates reproductive activation, which is associated with rising concentrations of gonadal hormones. Changing hormone levels act as a

trigger initiating a variety of neural mechanisms that stimulate sociosexual behavior and culminates in mating within 24-48 hours after pairing. The neuroimmune system, composed primarily of microglia and mast cells, is a critical regulator of many functions in the central nervous system. Microglia and mast cells are also exquisitely sensitive to gonadal hormones, suggesting that they may be key mediators bridging neuroendocrine activation and changes in sociosexual behavior. Previous research has shown that mast cell numbers increase in several brain regions in female prairie voles following exposure to male urine (a chemosensory stimulus that induces estrus). However, the potential role of microglia in reproductive activation and pair bond formation has never been directly examined. The objective of the current study was to analyze changes in microglia density and morphology in male and female prairie voles after being paired with a member of the opposite sex. We hypothesized that pair bonding and reproductive activation would be associated with increased numbers of microglia in brain regions implicated in sociosexual behavior, including the medial amygdala, anteroventral periventricular nucleus of the hypothalamus and medial habenula. Adult males and females were cohabitated with a novel member of the opposite sex, or remained housed with their sibling (controls), for 6, 30, or 54 hours. Brains and reproductive organs were collected immediately after cohabitations. Cohabitation with a novel male induced estrus in females, as indicated by uterine hypertrophy (30 and 54 hours) and the display of sexual receptivity (54 hours) compared to sibling controls and the 6-hour male-exposed group. Social interactions also differed between the two groups, as novel, mixed-sex pairs exhibited significantly more social investigation at the start of the cohabitation compared to sibling pairs. Both groups spent similar amounts of time huddling with one another; however, huddling was more active and combined with other activities (e.g., grooming and eating) in the newly-formed, mixed-sex pairs, whereas huddling in siblings was characterized by greater immobility. The effects of cohabitation on microglia number are currently being analyzed and will also be reported.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.12/OO14

Topic: F.02. Behavioral Neuroendocrinology

Support: Wabash College Special Psychology Fund

Title: Diet-induced obesity impairs male rat copulation and dopamine synthesis in the medial preoptic area

Authors: *N. DAO¹, H. E. WALSH², N. SCHMITZER-TORBERT¹

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Abstract: Rationale: High fat diet-induced obesity impairs male fertility via well-documented peripheral effects, but less is known about the impact of obesity on male central regulation of reproduction. Here we examined whether high fat diet-induced obesity affects male rat copulatory performance, and whether this effect is mediated by alterations in synthesis of gonadotropin-releasing hormones (GnRH) and dopamine in the hypothalamic medial preoptic area (MPOA). Methods: Adult Long Evans male rats were fed on a high fat diet (HFD; total calorie 21.92 kJ/g, including 13.15 kJ/g as fat) or a control diet (LFD; total calorie 16.10 kJ/g, including 1.61 kJ/g as fat) for 8 weeks. Rats were mated with an estrogen- and progesterone-treated (10µg/kg and 0.5 mg/kg, respectively) ovariectomized adult female, for 30 minutes after first intromission under red dim light. Behavior during mating was scored for total frequency of mounts (MF), intromissions (IF) and ejaculations (EF), latency to first mount (ML), first intromission (IL) and first ejaculation (EL), and intromission ratio (IR = IF/IF+MF). After an overnight fast, fresh MPOA tissues and blood samples were collected at decapitation for qRT-PCR of *Gnrh1* and tyrosine hydrolase (*Th*) and plasma glucose analyses. Results: HFD rats displayed higher total body weights, growth rate percentage and plasma glucose levels. HFD rats also showed fewer intromissions and ejaculations, and took longer to initiate first mount and first intromissions. Furthermore, there was a 0.48-fold reduction in mRNA expression of the dopamine-synthesizing *Th* in the MPOA. No change in *Gnrh1* mRNA expression was observed. There was also a trend for positive correlation between *Th* expression fold and copulatory parameters. Conclusion: Our data suggests that high fat diet-induced obesity impairs male rat copulatory performance, and this effect may be mediated by the dopaminergic system in the MPOA. As dopamine is involved in a range of motivated behaviors, including feeding and copulation, prolonged latency to mount and intromission and few mounting attempts therefore might reflect a diminished motivation to engage in sexual activity in obese animals.

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Poster

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.13/OO15

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: Fos expression in female rats with a conditioned partner preference for an individual male

Authors: *C. E. MAC CIONNAITH, A. LEMAY, E. GOMEZ-PERALES, G. C. ROBERT, R. CERNIK, J. G. PFAUS

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Abstract: A growing body of evidence shows important roles of Pavlovian learning in sexual partner selection. Female rats who repeatedly undergo paced copulation with almond scented males selectively solicit, and preferentially receive the scented male's ejaculations relative to those of an unscented male. Exposure to conditioned scented partner cues has been shown to induce Fos protein within oxytocin (OT) neurons in the paraventricular nucleus (PVN) of the hypothalamus. Whether female rats can be conditioned to show a partner preference for an individual male rat has not yet been shown. The aim of this study was to test whether female rats could form a conditioned preference for an individual male rat. Females were given paced copulation with either a one-hole divider or a four-hole divider in a unilevel pacing chamber but always copulated with the same partner during conditioning trials ($N = 32$). After 10 trials, females were then given an open-field partner preference test with the partner male and a novel male. Females underwent two reconditioning trials and were then exposed to the partner or a novel male for an hour to induce Fos protein, after which we examined regions of the brain associated with incentive motivation, sexual behaviour, and bonding (nucleus accumbens core and shell, medial preoptic area, and ventral tegmental area). Fos protein was also examined in OT-labelled neurons within the PVN and supraoptic nucleus (SON). Behavioural results indicated that females in the one-hole pacing group received the first ejaculation more frequently and more ejaculations overall from the partner male compared to the novel male. The four-hole pacing group did not display a conditioned partner preference. Preliminary counts in the PVN ($n = 3$) did not show a significant difference in Fos/OT co-labelled cells, but, there is a trend toward an interaction between the male females were exposed to and the pacing group ($p < .10$, $\eta^2 p = .141$). Preliminary results suggest this interaction is being driven by increased activation in females in the one-hole group exposed to the partner male. The behavioural data suggest that pacing is necessary but not sufficient for the formation of conditioned partner preference for an individual male rat. We expect that exposure to the partner in the one-hole pacing will show differential Fos expression compared to females exposed to a novel male and will not be present in the four-hole group. If this effect is found it would suggest that activation of OT cells in the PVN are likely involved in the display of conditioned partner preference for individual male rats as well as for conditioned odour cues.

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Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.14/OO16

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant HD042635

Title: The estrogen receptor- α splice variant, ER $\alpha\Delta 4$, negatively regulates estradiol signaling through mGluR2/3, *in vivo*

Authors: *A. M. WONG¹, C. S. JOHNSON², A. SCOTT¹, P. E. MICEVYCH³

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Abstract: ER $\alpha\Delta 4$, a 52 kDa alternative splice variant of estrogen receptor alpha (ER α) missing exon 4 from ESR1 mRNA, is present in plasma membrane fractions along with the full length ER α (65 kDa). In vitro, estradiol stimulation traffics and internalizes ER $\alpha\Delta 4$ from the plasma in parallel to full-length ER α . Steroid receptors are trafficked to the membrane by caveolin proteins. For ERs, caveolins (cav) also determine the association with particular metabotropic glutamate receptors (mGluRs) that mediate signaling. Caveolin-1 mediated the trafficking and association of full-length ER α with and mGluR1a leading to stimulatory signaling (e.g., release of internal calcium). We showed with co-immunoprecipitation that in membrane fractions from female rat hypothalamic arcuate nucleus (ARH) ER $\alpha\Delta 4$ associates with cav-3 and mGluR2/3. Microinjection of cav-3 siRNA into the ARH reduced membrane cav-3 and ER $\alpha\Delta 4$ proteins (50% and 60% respectively). Full-length ER α levels were not affected. Estradiol treatment reduced membrane levels of ER $\alpha\Delta 4$ as reflected by a reduced (40%) co-immunoprecipitation of mGluR2/3 and cav-3. Third ventricle injection of the group II mGluR antagonist, LY341,495 (25 μ g), followed by estradiol benzoate (EB; 10 μ g s.c.) attenuated the suppression of cAMP levels. In N-38 cells, an in vitro model of ARH neurons, we concluded that ER $\alpha\Delta 4$ signaled through mGluR2 since no mGluR3 mRNA was detected. We further examined whether ER $\alpha\Delta 4$ -mGluR2/3 mediated the estradiol downregulation of kisspeptin expression in the ARH. Third ventricular injection of LY341,495 prior to EB, did not prevent estradiol suppression of ARH kisspeptin expression. This was underscored by parallel immunohistochemical localization. mGluR2 was not colocalized with a marker of kisspeptin cells, dynorphin. However, mGluR2 was localized to NPY cells. While ER $\alpha\Delta 4$ transactivates mGluR2/3 to inhibit cell signaling in the ARH, there is no evidence that it mediates the downregulation of kisspeptin. Supported by HD042635.

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Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.15/OO17

Topic: F.02. Behavioral Neuroendocrinology

Title: Investigating the role of dopamine in steroid-independent male sexual behavior in orchidectomized B6D2F1 hybrid male mice

Authors: *C. D. DAVID, B. N. WYROSDIC, R. M. A. ABBAKER, J. PARK
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Abstract: Male sexual behavior (MSB) is tightly regulated by gonadal steroids in many mammalian species; however, individual differences in MSB are prevalent, and the mechanisms underlying these differences are poorly understood. Approximately 30% of B6D2F1 hybrid male mice retain MSB after long-term castration, providing a mouse model with which to study MSB in the absence of steroids. Additionally, dopamine (DA) in the medial preoptic area (mPOA), a major nucleus for MSB, subserves a combination of functions related to MSB. Several lines of research investigating crosstalk between steroids and neurotransmitters provide compelling evidence that dopamine may facilitate MSB in the absence of ligand. Thus, the present study investigates whether DA plays a significant role in steroid-independent MSB in B6D2F1 hybrid male mice. Briefly, sexually experienced male B6D2F1 mice were orchidectomized, tested biweekly for MSB (6 tests), categorized and assigned to treatment groups, and tested an additional three times with drug administration. Males were categorized as “maters” (displayed an ejaculation on at least 2 of tests 3-6; n=13) or “non-maters” (did not ejaculate on tests 2-6 nor intromit on more than 1 of tests 2-6; n=11). Maters were then randomly assigned into groups that received either a subcutaneous injection of dimethyl sulfoxide (DMSO) or DA antagonist haloperidol (50 µg/kg dissolved in DMSO), and non-maters were randomly assigned into groups that received either a subcutaneous injection of saline (0.9% NaCL) or the DA agonist apomorphine (7.5 µg/kg dissolved in saline). Among the maters that received either haloperidol or vehicle, there was a significant decrease in steroid-independent MSB in both groups, suggesting that injection stress may significantly impact steroid-independent MSB. This conclusion was supported by a pairwise comparison that revealed a difference between mean intromission and ejaculation latencies before and after drug administration among both haloperidol-treated and control-treated maters ($p < .05$). Additionally, administration of apomorphine did not facilitate steroid-independent MSB among the non-maters. Future studies will benefit from considering differential effects of stress on maters and non-maters that may preclude understanding the role of dopamine in steroid-independent MSB.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Program #/Poster #: 066.16/OO18

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT fellowship 277930 VRP
PDCBS 2014-2018 UAMI

Title: Sexual satiety modifies the tissue characteristics of the prostatic lobes in male rats

Authors: *V. RODRÍGUEZ¹, M. GARCÍA-LORENZANA², Y. CRUZ³, R. A. LUCIO⁴

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Abstract: Male rats presents ventral (VL), lateral (LL) and dorsal (DL) prostatic lobes that differ in their secretion and alveolar tissue organization. Prostatic secretions contribute to the formation of seminal plasma. This plasma and the sperm make up semen that decreases with successive ejaculations. Around 5-8 ejaculatory series are required to reach sexual satiety (copulatory inactivity during 30 minutes after the last ejaculation). Recently, the ejaculate (semen+seminal plug) has been analyzed at different postsatiety days (PSD). At 5 PSD, males perform the ejaculation pattern without ejecting semen. At 10 PSD, rats expel semen but plug is not adhered to the vagina. At 15 PSD, the plug adhered to vagina facilitates the transcervical sperm transport. Thus the aim was to analyze morphometric changes of prostatic lobes during the recovery of sexual satiety. Wistar rats were used (females with induced estrus, sexually experienced males). Males were allowed to execute one ejaculatory series (non-satiated) or ejaculate until sexual satiation. Later satiated males were sacrificed at 0, 4, 8, 12, 16, 20, 24 PSD. Prostatic lobes were excised and processed using the routine histological methods. Hematoxylin-Eosin was used to stain tissue sections of 5 µm of thickness. The VL of non-satiated rats presented different sizes of alveoli with folds and irregular lumen, simple cylindrical epithelium lines alveoli containing acidophilic secretion. Males at different PSD showed folds and simple cylindrical epithelium, only at day 8, 12 and 16 some regions of alveoli presented simple cuboidal epithelium. At day 0 some alveoli lack secretion, at day 16 the secretion occupied 80-100% of the lumen. The LL of non-satiated males and satiated ones at different PSD present few folds and simple cuboidal epithelium, the acidophilic secretion occupies the lumen completely. The DL of non-satiated and satiated males showed folds, with simple cuboidal epithelium, at 4 PSD the secretion occupied 50% of lumen. While more PSD elapsed, the secretion covered more lumen (70%, 100% at 12, 20 respectively). The height of epithelial cells of the VL immediately satiation was greater than the non-satiated, but at 12 PSD decreased respect to the non-satiated. The height of epithelial cells of the LL and DL were reduced at first days of sexual satiation. Later they increased at the same height of the non-satiated. Each prostatic lobe showed different activity, therefore, their tissue reorganization was heterochronic, first VL followed by LL and DL coinciding with the adhesion of the seminal plug to the vagina to induce sperm transport to uterus.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Program #/Poster #: 066.17/PP1

Topic: F.02. Behavioral Neuroendocrinology

Title: CRISPR/Cas genome editing identifies prostaglandin F sensitive cells as crucial regulators for the control of reproductive behavior in the cichlid *Astatotilapia burtoni*

Authors: *S. A. JUNTTI

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Abstract: Across the animal kingdom, hormones coordinate the physiology of diverse tissues. In the brain, these signals exert powerful influences on behavior. Therefore, hormonal control of fascinating behavioral displays exhibited in numerous species offers a tantalizing entry point to understand brain function. However, for the majority of species, it has been difficult to gain a mechanistic understanding of the cellular processes at work due to technical constraints. Recently, CRISPR/Cas9 has emerged as a potent tool for manipulating the genome of any species desired, in principle. The cichlid fish family displays a wide range of social behaviors that are regulated by hormonal signals. I describe the use of CRISPR gene editing in the cichlid *Astatotilapia burtoni* to manipulate prostaglandin F (PGF) signaling. Combining molecular genetics with behavioral analysis and other tools, we dissect the molecular genetic control of social behavior in *A. burtoni* to show that PGF signaling is necessary and sufficient for female sexual behavior. Our work shows that the cells sensitive to PGF are central nodes in the female behavior circuit that is responsive to a variety of hormones. We extend this work through candidate gene approaches, whole-transcriptome brain sequencing, transgenesis and CRISPR to identify and test genetic components of neural circuits that regulate a variety of social behaviors.

Disclosures: S.A. Juntti: None.

Poster

066. Neuroendocrinology of Sexual Behavior

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Program #/Poster #: 066.18/PP2

Topic: F.02. Behavioral Neuroendocrinology

Support: SEP-CONACYT (167773)

Title: Effects of testosterone and quinpirole (D2-type agonist) in adulthood on the sexual partner preference of neonatally gonadectomized male rats

Authors: *M. BARRADAS^{1,2}, D. HERRERA COVARRUBIAS¹, L. GARCÍA¹, P. CARRILLO¹, J. MANZO¹, G. CORIA-AVILA¹

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Abstract: The organizational-activational theory (Phoenix et al., 1959) proposes that the brain is masculinized during a critical perinatal period of development following exposure to fetal androgens. Then, during puberty, it is activated by gonadal androgens to modulate sexual behavior. Accordingly, males that fail to receive sufficient androgens perinatally may display abnormal masculine organization of the brain and the corresponding abnormal male sexual behavior in adulthood. Thus, in experiment 1 we tested the effects of early gonadectomy (EGx) on the sexual partner preference displayed in adulthood. Male rats were divided in the following groups: 1) EGx, castrated under inhaled fluothane at 1 day of age (PD1). 2) sham operated; 3) gonadally intact, and 4) EGx + testosterone (T, 5 mg/kg/sc every 48 h) from PD30 to PD60. At PD21 they were weaned and housed in groups. At PD60 sexual preference was tested before a male and a sexually receptive female. The results showed that males from the group EGx displayed more visits towards the male partner, displayed more olfactory investigations, more genital investigations, received mounts from him, failed to display intromissions, and expressed less non-contact erections in general. These effects were not observed in the EGx+T group, suggesting that the effects depended on the presence of systemic testosterone, but not on organization of the brain. Then for experiment 2, each group was subdivided in either treated with saline or quinpirole (1.25 mg/kg) during cohabitation with a sexually receptive female for three trials. Then, four days after the last cohabitation trial their partner preference was tested again at PD90 in a quinpirole-free trial. The results showed that EGx+quinpirole males (but not EGx+saline) preferred females for olfactory investigations, genital investigations and mount attempts, but no effect of quinpirole was observed in visits, contacts, intromissions, ejaculations, time spent visiting, or non-contact erections. Taken together, these results indicate that gonadectomy at PD1 does not affect the long-term masculinization of the brain. Interestingly, impaired adult sexual preference of EGx males was partially reversed by cohabitation with receptive females under the effects of the D2-type agonist, suggesting that sexual learning that occurs under the effects of D2-type agonist is, to some extent, independent of the presence of systemic testosterone. keywords: quinpirole, D2, dopamine, partner preference, sexual motivation, testosterone, gonadectomy.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Program #/Poster #: 066.19/PP3

Topic: F.02. Behavioral Neuroendocrinology

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Fronteras 374
UNAMDGAPA- PAPPIT

Title: When sexual hormones are not enough. Role of sexual experience in female mice receptivity

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Abstract: Sexually naïve female mice display low levels of sexual receptivity in their first sexual experience. Hormones induce sexual receptivity, but they are not sufficient to increase receptivity, sexual experience is required. Sexual receptivity is observed when females display lordosis, in which they flex their back exposing the genitalia and facilitating penile penetration. It is quantified by the lordosis quotient (LQ, number of lordosis displayed/number of mounts). In the present study we aimed to determine if an overdose of estradiol (E2) and progesterone (P) is sufficient to increase sexual receptivity. We also evaluated if sexual experience induces changes in the activity, determined by c-Fos expression, of brain areas that modulate this behaviour such as: the accessory olfactory bulb (AOB), the Medial Preoptic Area (MPOA), the Ventromedial Hypothalamus (HVM) and the Amygdala (AMG). 60 CF1 ovariectomized female mice were assigned in one of the following groups: Experienced females (n=20), which received 6 mating sessions; Unexperienced females (n=18), which receive only 1 mating session; and Naïve females (n=18), which had no previous sexual experience; and Hormone Overdose group (n=6). Mating sessions lasted 1h registering different behavioural parameters. Females were hormonally primed with 1 µg of estradiol and 100 µg of progesterone (48h and 4h respectively, before the test), except for the overdose group which receive 10 µg of E2 and 1 mg of P. All females received 6 injections of each hormone to make groups comparable. Each group was divided in 3 subgroups: Mating group, which receive a 7th mating session; Olfaction group, exposed to bedding from sexually experienced males and Control group, subjects were exposed to clean bedding for 90 min after the last test. Animals were euthanized and perfused, and their brains were collected and sliced. Brain sections were immunostained for c-Fos. Our results show that sexual experience increases the number of c-Fos+ cells in the VMH, and decrease them in the

MPOA in Unexperienced females (but not in the Experienced). In the VMH the number of cells correlated with the LQ of the subjects. In all the layers of the AOB a higher number of c-Fos+ cells was observed when females were exposed to male odorants. But this increase was not seen when the females mated. In the Anterior Cortical Amygdala a reduction of c-fos+ cells were observed only when females were exposed to male odorants. Our results suggest that high levels of sexual receptivity depend on the experience and not only of the hormonal treatment. Sexual experience increases the number of c-fos+ cells in the VMH and decreases the number of c-Fos+ cells in the MPOA and AOB.

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Poster

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Fronteras 374

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PAPITT-DEGAPA 210215

Title: Effects of pair bond formation in prairie vole brain functional connectivity

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Abstract: *Microtus ochrogaster*, the prairie vole, is an animal model whose natural behavior enables the study of human-like social interactions. The formation of enduring social bonds in both humans and voles, plays an important role in their wellbeing and has a direct impact on their descendants.

It has been found that pair bond formation in the prairie vole is associated with changes in brain plasticity, including increased electrophysiological activity and neurotransmission in several brain regions, such as nucleus accumbens (NAcc) and the medial prefrontal cortex (mPFC). However, the interaction and involvement between the former and other socio-sexually relevant

regions has yet to be described.

Through functional magnetic resonance imaging (rsfMRI), resting state networks have already been characterised in this model, including putative salience and default mode networks. The application of this non-invasive technique allows the analysis of multiple regions and network components, which may find changes in functional connectivity before and after pair bond formation in brain regions of male and female prairie voles.

In this study we obtained rsfMRI data from male and female prairie voles before pair bond formation, and 24h and 15 days after pair bond formation. What we found is an increase in functional connectivity between NAcc and Medial Amygdala (MeA) ($T = 2.3195$; $p < 0.05$) 24h after pair bond formation, and an increase between NAcc and Ventral Tegmental Area (VTA) ($T = 2.8991$; $p < 0.05$) after 15 days of pair bonding in both male and female voles. Interestingly, there was also a decreased functional connectivity between the Paraventricular Nucleus (PVN) and MeA ($T = -2.0808$; $p < 0.05$) 24h after pair bonding; and 15 days after, a decrease between PVN and NAcc ($T = -2.7320$; $p < 0.05$) in both sexes.

These preliminary results indicate dynamic changes in functional connectivity in regions relevant for pair bond formation and sexual behavior in male and female prairie voles.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

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Fronteras 374

PAPITT IN210215

Title: Standardization of MEMRI to study brain regions involved in sexual behavior

Authors: *J. A. AGUILAR MORENO¹, J. ORTIZ², D. GASCA³, S. ALCAUTER², R. PAREDES-G¹

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Abstract: Magnetic resonance imaging (MRI) is a powerful tool to perform longitudinal studies while measure brain changes without the sacrifice of the subject. Functional brain activity can be traced combining MRI with chloride manganese (MnCl₂) administration (24hrs before scanning). MnCl₂ enters the excited cells modifying the local magnetic field, making possible to

measure the activation of brain areas activated by behavior. At high doses manganese can induce neurotoxicity, affecting the motor skills of the animal. In our lab we demonstrated that sexual behavior (SB) induces permanent brain plastic changes when the female rat can pace the sexual interaction. In the present experiment we wanted to determine the dose of MnCl₂ that will not induce behavioral alterations to further evaluate the brain circuits activated by sexual behavior. We used 45 female Wistar rats, 250-300grs, without sexual experience. They were ovariectomized and supplemented with hormonal treatment to induce receptivity and proceptivity and randomly assigned to one of the following groups: Control (saline), MnCl₂ 8mg/kg and MnCl₂ 16mg/kg. Females were tested for sexual behavior in conditions where they control the rate of sexual interaction (paced) for 30 minutes. Immediately thereafter they were exposed for 30 minutes to a running wheel. Finally, they were evaluated in a rotarod. Subjects were tested in the same behavioral sequence once a week for 10 weeks. MnCl₂ was administered s.c. on sessions 1, 5 and 10. An additional group was injected with the same MnCl₂ indicated doses and tested for sexual behavior in the same time as the other groups and scan in weeks 1, 5 and 10. The results show that none of the doses tested interfere with SB or produce motor alterations in the female rats. The statistical maps of MEMRI showed a significant brain activation in the olfactory bulb, amygdala, medial preoptic area in the experimental groups in session 5 (8mg/kg, p<0.05) and 10 (8mg/kg and 16mg/kg, p<0.01). The results demonstrate that 8mg/kg and 16mg/kg of MnCl₂ are adequate doses to study SB with MEMRI without behavioral alterations.

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Poster

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Title: Partner preference in the female monogamous prairie vole *Microtus ochrogaster* tested in a multiple partner paradigm

Authors: *A. FERREIRA-NUNO¹, F. J. CAMACHO², L. J. YOUNG³, R. G. PAREDES², W. PORTILLO²

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Abstract: The prairie vole (*Microtus ochrogaster*) is one of the few species of mammals with a social monogamous reproductive strategy. Once the voles mate for a 6 h period, they form an enduring pair bond. In this study, we analyze their mate choices and the role of familiar kinship. For this goal we use a Multiple Partner Paradigm made with 4 Plexiglas cylinders arranged in a cross formation. Each cylinder has a hole on the floor allowing the females to go back and forth from each cylinder to the central security compartment naturally formed by the alignment of the 4 cylinders. In each cylinder we placed a tethered male with one of the following characteristics: a) father, b) brother, c) cousin and d) not family, unrelated male for each experimental female (n = 7). Females and all the stimulus males except for the father were sexually naïve. Females were primed with estradiol benzoate (0.5µg/vole) for 4 consecutive days to induce sexual receptivity and were introduced into the central compartment allowing them to interact with the 4 stimulus males for 6h. The test was videotaped, and the following parameters recorded during the first and the last hour of the test: time spent and number of visits to each male, the number of mounts, intromissions and ejaculations and huddling time. These parameters allowed us to establish the preferred male. We hypothesized that if in this species there is a mechanism to avoid consanguinity as it happens with other rodents, the female should prefer and pair bond with the unrelated male. Our result shows that during the first hour females interact actively with the 4 males. As expected, the father showed aggressive behavior to the females. Interestingly, 6 females out of 7 selected the cousin as preferred male, spending more time and receiving more sexual contacts from him. Apparently, as it has been observed in other rodents, voles prefer the cousin as a partner to preserve the genetic information that has been accumulated during the evolution of this species.

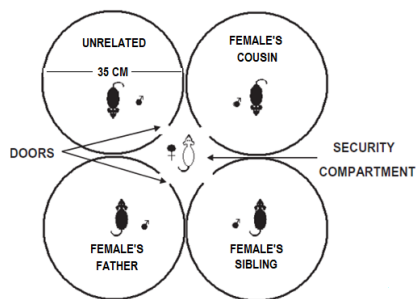


Figure 1. Multiple Partner Paradigm made with four transparent acrylic cylinders (35 cm, wide). Each compartment has an entry door in their base directed to the central security compartment. Four male voles with a different kinship regard the experimental female placed in the central compartment, were tethered inside each cylinder.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: Palatin Technologies

Title: Influence of acute bremelanotide following chronic administration of fluoxetine on 50-kHz vocalizations during distributed clitoral stimulation

Authors: *C. A. GERSON, L. SPARKS, B. V. GONZALEZ CAUTELA, J. G. PFAUS
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Abstract: Fluoxetine (FLU) is a commonly prescribed selective serotonin reuptake inhibitor shown to cause anorgasmia and loss of libido in women. A synthetic melanocortin analog of melanocyte-stimulating hormone known as bremelanotide (BMT) has been purposed to alleviate the loss of libido by increasing sexual desire. Pre-clinical trials with female rats show that sexually appetitive behaviors decrease with chronic FLU subcutaneous administration and increase with acute BMT subcutaneous administration. One behavioral measure not included in these trials is 50-kHz ultrasonic vocalizations (USV), which are suggested to be indicative of a positive affective state and reward state. Adult rats emit 50-kHz in response to reward stimuli during appetitive situations such as mating and distributed clitoral stimulation (CLS). The administration of CLS in conjunction with sufficient hormonally priming has previously been shown to increase temporal parameters of 50-kHz USV of the trill and the flat-trill subtype. The present study examined the effects of chronic FLU (daily 10 mg/kg) on the emission of CLS-related trills and flat-trill call profile and whether acute BMT (0.2 mg/kg/ml) could reverse decreases of this call profile induced by chronic FLU. The effects of CLS on the expression of appetitive sexual behaviors prior to paced copulation trials were also examined. Ovariectomized females were randomly selected to receive CLS during USV recording 1 hour prior to paced copulation trials. Those selected not to receive CLS were not recorded. Vocalization recordings were conducted 1 hour prior to paced copulation trials and were recorded at drug baseline and, throughout FLU and FLU + BMT administration during CLS, which was made by lightly brushing the clitoris using a No. 4 paintbrush. CLS was applied every 5 sec for 1 min after a 4 min no-CLS recording block and this was repeated for 7 cycles for total session duration of 35 minutes. Spectrotemporal parameters of recorded USVs were analyzed before, during and after each bout of CLS. At drug baseline, primed females demonstrated USVs emission during CLS administration like our previous report. Chronic FLU decreases spectrotemporal parameters of CLS related calls compared to drug baseline. Solicitations and lordosis magnitude were slightly but significantly increased in FLU treated females who received CLS prior to copulation trials

relative to females who received no CLS. Acute BMT increased CLS-related calls but did not return call emission to drug baseline.

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Poster

066. Neuroendocrinology of Sexual Behavior

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Topic: F.02. Behavioral Neuroendocrinology

Support: BUAP/MORC-NAT86-I-1
CONACYT/624536

Title: The catecholamines synthesis and the morphometry of the ovarian intrinsic neurons in the senescent rats

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Abstract: The nerve terminals in the ovaries regulate processes like reproductive cycles, follicular development, ovulation and steroidogenesis. In the Wistar rat, the intrinsic innervation of the ovary is provided by neurons with multipolar soma into the ovary. The aim of the present study was to identify the intrinsic neurons into the ovaries in the CIIZV strain (Sprague Dowley), through the analysis of their morphological and biochemical characteristics and their role in the senescence process. Adult female rats of 3 and 15 months of age were used, those which were

maintained in biotarium conditions and sacrificed by intracardiac perfusion. The ovarian tissue was cut into sections of 7 μ m thickness at -20 °C. Immunohistochemical identification was performed using the Neu-N and Tyrosine Hydroxylase (TH) antibody. To make observations and analysis of immunoreactivity to antibodies in the ovaries it was used a fluorescence microscope (Olympus BX41). The results showed immunoreactivity to Neu-N and TH around the follicles and in the interstitial gland. In 3-month-old animals, the diameter of neurons is 8.7 \pm 0.14 μ m, while animals of 15 months of age, was 12.19 \pm 0.14 μ m (p <0.01 Student's T test). In the three-month-old, the mean area of the immunoreactive cells was 63.42 \pm 2.1 μ m², while for the 15-month-old animals it was 129.13 \pm 8.3 μ m² (p <0.001 Student's T test). We can advance that in the follicular theca layer and interstitial gland the presence of neurons is closely related to the ovarian follicles, which synthesize tyrosine hydroxylase and has a different morphometry in the senescent ovary.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Title: Effects of developmental exposure to bisphenol-S on sexual behavior in female rats

Authors: ***H. A. MOLENDIA-FIGUEIRA**, A. T. DUFFIN, K. R. GRIMES, D. T. LARSON, B. A. LENZ, K. R. MAKOVEC, T. J. POZOLINSKI, M. E. RACINE, T. A. TAUBER
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Abstract: Developmental exposure to endocrine disruptors may play an underlying role in a diverse group of disorders, ranging from cancers to anxiety, attention deficit hyperactivity disorder, neurodegeneration and Schizophrenia. Bisphenol-S (BPS) is an endocrine disrupting chemical that has replaced BPA in many household products, but it is unclear whether it is a safe alternative. Previous studies have demonstrate that BPS exposure negatively affects gamete production and hormone secretion in male rodents and zebrafish, however, the effects of this chemical on female rodent reproduction remains largely unexplored. We investigated the impact of developmental BPS exposure on reproduction in female Long-Evans rats. Rats were paired with stud males on the day of estrus as determined by vaginal cytology. BPS was administered orally via pipette to each dam at a dose of 50 μ g of BPS in 0.3% saline vehicle /kg body weight/day beginning on the day of pairing and continuing until parturition. Control dams received saline. Female pups were treated with BPS or saline beginning on the day after birth and continuing until 45 days of age to encompass puberty, a developmental time point when

disruption of normal hormone function can lead to negative consequences for adult sexual behavior in rodents. Once females reached 60 days of age, vaginal cytology was assessed daily. When determined to be in estrus, sexual behavior tests were conducted under dim red light during the dark phase of the 14:10 LD cycle. Each female was paired with a male stud rat and behavior video recorded. For each mount, the intensity of the lordosis posture and number of proceptive behaviors (hops, darts and ear wiggles) were recorded by observers blind to the treatment. The average lordosis intensity, lordosis quotient and total number of proceptive behaviors were quantified, and data analyzed using a 2-tailed *t*-test. We found that developmental exposure to BPS decreased the intensity of the lordosis posture, however, no differences were found between BPS- and control-treated rats for the lordosis quotient or proceptive behaviors. These findings indicate that BPS may disrupt the development of neural circuits controlling the lordosis posture, perhaps decreasing the sensitivity of this circuitry to the effects of ovarian hormones when female rats are in estrus.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT 306451 (MRFM)

Title: Sexual behavior, ejaculate and fertility of rapid ejaculators during copulatory competition

Authors: *M. R. FUENTES MORALES, SR¹, G. GUTIÉRREZ OSPINA², J. A. FERNÁNDEZ GUASTI³, R. LUCIO⁴

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Abstract: Men and male rats present biological variability in the ejaculation latency (EL). In both populations exist rapid, normal and slow ejaculators. It has been suggested that variations in EL depends on a neurobiological substrate. If this is true, the EL of rapid ejaculators (RE) must be invariable. However, EL is shorten by male competition, at least in mice. Thus a question arises, do RE rats can short their EL? In another hand, seminal characteristics depends on the sexual context. Thus, what happen with the ejaculate of RE rats during male competition? It is evidenced that a single ejaculation with multiple intromissions are required to induce pregnancy.

Therefore, if EL of RE is shorten and seminal characteristics change, how will the fertility of theses males? Wistar rats were used. After a copulatory training males were identified as RE, and were allowed to one of two copulatory contexts: 1) Copulation without-competition: one male/one female or 2) Copulation with-competition: two males/one female. In each context the copulatory parameters (NI= number of intromissions, EL, and III=inter-intromission interval), seminal parameters (sperm count, sperm motility and weight of copulatory plug), and fertility parameters (number of pregnant females and pups) were evaluated. We observed that copulation with-competition decreased the EL, NI and III (179.2 ± 28.5 sec, 6.8 ± 0.4 , 26.7 ± 4.9 sec, respectively) compared to values without-competition (376.0 ± 39.87 sec, 9.0 ± 0.61 , 52.86 ± 10.31 sec, correspondingly). Respect to the ejaculate, sperm count increased ($100.9\pm 11.5\times 10^6$ vs $38.3\pm 6.7\times 10^6$), and sperm motility was abolished ($5.1\pm 3.06\%$ vs $76.8\pm 3.9\%$) in RE with competition vs without competition, correspondingly. The seminal plug weight remained unchanged (113.7 ± 7.3 vs 110.2 ± 7.9 mg). RE rats pregnant a smaller number of females (55.5% vs 80%) during competition vs copulation without-competition. However, the number of pups in both copulation context were similar (9.0 ± 1.9 vs 6.7 ± 2.2). In conclusion, the EL of RE male rats is not fixed, it diminished due to male copulatory competition. Reduced EL of RE abolished sperm motility. Thus, effectively, the characteristics of the ejaculate depends on the copulatory execution. The reduced EL and NI, and the poor sperm motility of RE, during competition, resulted in the low percentage of pregnant females. It is possible the existence of internal female mechanisms that activate sperm motility, which would explain an equivalent number of pups. CONACYT fellowship 306451 (MRFM).

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Poster

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Program #/Poster #: 066.27/PP11

Topic: F.02. Behavioral Neuroendocrinology

Title: Practice makes perfect: Repeated sexual experience enhances sexual motivation as female rats approach middle-age

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Abstract: Reproductive senescence is an inevitable aspect of female aging. Nevertheless, our understanding of how sexual behavior changes across the lifespan is limited. The current study investigated the effects of repeated sexual experience as female rats approach middle age (12

mos. old). Females rats (aged experienced; n=10) were tested for partner preference (2x per month, from young adulthood to middle age). In the partner preference test, each subject is given the choice to interact with a same-sex conspecific or a sexually vigorous male, which allows for the opportunity to mate. With repeated tests, female rats increased time spent with the male, displayed more solicitation behaviors, and were less likely to leave the male after mounts. However, female rats became less active over time, visiting the stimulus animals less frequently. A separate group of age-matched, hormone-yoked female rats (aged virgins; n=11) were left to age alongside the sexually-experienced group and then mated for the first time at 12 mos. old when the experienced group received their final mating test. Aged virgins spent significantly less time with the male and displayed fewer solicitation behaviors than their experienced counterparts. We also compared mating behavior on the first test of young adult rats (young virgins, 2 months old) to the first test of middle-aged rats (aged virgins, 12 months old). Aged virgins took longer to return to the male after intromissions and displayed fewer solicitation behaviors than young virgins during their first sexual encounter. Finally, aged virgins were less active, visiting the stimulus animals less frequently than young virgins. Taken together, these results suggest that repeated mating encounters increase sexual motivation, even as females transition into middle age and that delaying the first mating encounter until middle age leads to reduced sexual motivation relative to a first mating encounter as a young adult. We also found a number of specific effects of aging on partner preference. In summary, these findings add to our understanding of changes in reproductive behavior across the lifespan.

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Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 066.28/PP12

Topic: F.02. Behavioral Neuroendocrinology

Support: conacyt 167773
conacyt 429610

Title: Prenatal acetaminophen disrupts adult male sexual behavior: Partial recovery following sexual experience

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Abstract: Sexual dimorphism of the brain depends on a neuroendocrine cascade that includes production of gonadal testosterone, aromatization to estrogen in the brain, activation of prostaglandin receptors, activity of certain kinases and type 2 cyclooxygenases (COX-2). Blockade of any of these processes during critical periods of development impairs sexual brain dimorphism, and may affect sexual behavior in adulthood. Thus, we tested the effects of acetaminophen (paracetamol), which is commonly given to pregnant women during the last trimester. This drug mainly acts as pain killer by inhibiting prostaglandin activity and COX-2. Accordingly, we hypothesized that male rats treated prenatally with acetaminophen would display abnormal male sexual behavior in adulthood. Accordingly, Wistar female rats received either Acetaminophen (50mg/kg/ml) or Saline (1ml/kg) subcutaneously from day 16 to 20 of pregnancy. At postnatal day P60 the unconditioned preference was tested before an adult male and a sexually receptive female. The results indicated that Acetaminophen-treated males did not display same-sex preference, but express poor sexual performance and interest when compared with saline-treated males (e.g. visits, body contacts, olfactory investigations, mounts), but higher frequency of non-contact erections. Then half of each group was exposed to sexually receptive females during five trials to gain sexual experience, and the other half remained unexperienced. At P90 they were tested for conditioned preference. The results indicated that sexual experienced reversed only some impairments of sexual behavior (e.g. visits, total time spent visiting, genital investigations, mounts). These results indicate that prenatal acetaminophen impairs sexual behavior of adult males, and that there is a partial recovery following sexual experience.

Disclosures: **G.A. Coria-Avila:** None. **V.X. Díaz-Estrada:** None. **M. Barradas:** None. **L.I. Garcia:** None. **J. Manzo:** None. **G. Hernandez Peredo Rezk:** None. **D. Herrera-Covarrubias:** None.

Poster

066. Neuroendocrinology of Sexual Behavior

Location: SDCC Halls B-H

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Topic: F.02. Behavioral Neuroendocrinology

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Title: Raised without a father: Monoparental care impairs the preference for opposite sex odors in female prairie voles, but not in males

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Abstract: In most modern societies fathers are increasing their engagement in the raise of their children resulting in behavioral, emotional and cognitive benefits for the progeny. However, the neurobiological advantages of biparental care are not well understood. *Microtus ochrogaster*, the prairie vole, is an ideal species to study biparental care (BP) because they build a strong pair bond and share the care of the offspring. Voles raised only by their mother (monoparental, MP) need more time as adults to build a pair bond. We evaluated if the delay in pair bond formation is a consequence of alterations in the amount of parental care received, or deficits in olfaction and/or sexual behavior when adults. Our results show that BP raised pups were more frequently licked ($p < 0.05$, $F_{1,15} = 4.778$) than MP voles. When adult, both groups of male and female voles were able to discriminate between different odors ($p < 0.001$) but MP females didn't show preference for male-soiled bedding ($F_{2,18} = 1.779$, $p > 0.05$) as biparental females did ($F_{2,18} = 14.333$, $p < 0.001$). No differences were found in the anogenital sniffing or sexual receptivity between female groups. No differences were found between male groups in their preference for female-soiled bedding or their sexual behavior with receptive females. Our experiments demonstrate that monoparental rearing decreases the preference for male odors in the females but doesn't impair mating in male or female voles.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.01/PP14

Topic: F.04. Stress and the Brain

Support: KAKENHI JP 16K13017

Title: Monoaminergic systems contribute to decision-making in the familiar choice task just after acute mild stress

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Abstract: Extensive evidences have indicated that acute stress influences decision-making even under familiar choice situations, but the neural mechanisms are still unclear. Several studies have suggested that monoaminergic projections from the brainstem to the prefrontal cortex and amygdala can modulate the decision-making processes. The monoaminergic neurons, including serotonin neurons in the dorsal raphe nucleus (DRN 5-HT), noradrenaline neurons in the locus coeruleus (LC NA), and dopamine neurons in the ventral tegmental area (VTA DA), are also known to be sensitive to various stressor. Thus, it is possible that monoaminergic systems may be involved in the effects of acute stress on decision-making. Here, to examine the involvement of monoaminergic systems in decision-making immediately after an acute mild stress, we assessed choice behaviors and neural activity of DRN 5-HT, LC NA, and VTA DA neurons, which relate to impulse, attention, and reward control respectively, as well as stress responses, in T-maze task in rats. In the T-maze choice task, an arm has 3 pellets (high-reward side) and the other arm has 1 pellet and the high-reward side was constant throughout the maze test for each rat. As a familiar choice task, rats ran the task under the same reward condition three consecutive days. Before starting the 3rd day session, rats in the stress-treated group received mild restraint stress for 30 min, and rats in the control group were left in a normal cage. On the 3rd day session, we recorded the number of choice of high-reward side and vicarious trial-and-error (VTE) at the T-shaped choice point. Previous studies have reported that VTE is rat's head-orienting behavior toward possible options at choice points, and reflects deliberative, or less decisive, states of rats in decision-making. In addition, we quantified neural activity of the monoaminergic neurons, using c-Fos/5-HT or c-Fos/TH (tyrosine hydroxylase) immunohistochemistry. Acute restraint stress just before the choice task did not affect the number of choice of high reward-side, but the number of VTE was increased during the session after the acute stress. The activity of the DRN 5-HT, LC NA, but not VTA DA neurons, were increased in the stress treated group compared to the control group. These results suggest that monoaminergic systems contribute to decision-making in the choice task in a familiar situation just after acute mild stress. Namely, acute mild stress seems to increase a deliberate tendency in decision-making via activating monoaminergic systems related to impulse control and attentional control.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 067.02/PP15

Topic: F.04. Stress and the Brain

Support: NIH Grant DK100685
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Title: Acute amphetamine-induced activation of chemically-identified neurons within the rat nucleus of the solitary tract (NTS)

Authors: *C. M. EDWARDS, H. ZHENG, L. M. RINAMAN
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Abstract: Similar to other reinforcing drugs of abuse, amphetamine (amph) seems to have additional aversive components. Rats will self-administer amph, but amph also suppresses food intake and induces conditioned taste avoidance (CTA), a form of associative learning in which a novel taste (conditioned stimulus; CS) is paired with a viscerally aversive state (unconditioned stimulus; US), leading to subsequent avoidance (i.e., reduced preference and intake) of the CS. Thus, amph may act as a homeostatic stressor to promote both hypophagia and CTA. The NTS receives vagal sensory signals conveying feedback about internal state, and NTS neurons project to the hypothalamus, parabrachial nucleus (PBN), and other brain regions implicated in food intake, avoidance, and other motivated behaviors. Noradrenergic (NA) and glucagon-like peptide-1 (GLP-1) NTS neurons are recruited by aversive cognitive and physical stimuli, and thus, are prime candidates for being recruited by amph to induce its aversive effects. Additionally, recent studies using genetically-engineered mice demonstrated aversive CTA-inducing effects of opto- or chemogenetic activation of CCK-expressing NTS neurons. Therefore, we hypothesized that NA, GLP-1, and CCK neurons within the NTS are recruited by acute amph treatment. Interestingly, amph-induced CTA and hypophagia are reduced by prior food deprivation, which we previously reported to attenuate stress-induced hypophagia and activation of NA and GLP-1 neurons. Thus, we also examined whether amph-induced NTS activation is suppressed after food deprivation. Activation of cFos within the NTS was quantified in adult male Sprague-Dawley rats (n=24) that were fed ad-lib or food deprived overnight before i.p. injection of vehicle or amph (3mg/kg). Amph robustly activated NTS neurons, including NA and some CCK neurons. Conversely, amph did not activate GLP-1 neurons. Amph also robustly activated cFos within the lateral PBN and central amygdala. Food deprivation did not alter amph-induced activation of NA or CCK neurons, or NTS neurons in general. Our results indicate that NA and CCK neurons within the NTS are recruited by acute amph treatment independent of metabolic status, and may contribute to amph-induced activation of PBN and amygdala neurons that have been implicated in CTA.

Disclosures: C.M. Edwards: None. H. Zheng: None. L.M. Rinaman: None.

Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 067.03/PP16

Topic: F.04. Stress and the Brain

Support: Sasakawa Scientific Research Grant 26-646

Title: Housing conditions influence characteristic of voluntary exercise and brain monoamine levels in laboratory rats

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Abstract: In animal studies, wheel running is a common experimental model of voluntary exercise. Previous studies have revealed that amount of wheel running is a key for beneficial effects of voluntary exercise on brain health. These animal studies with wheel running have conventionally used individual housing condition to correctly record the amount of wheel running in spite of the fact that laboratory rodents are usually housed in small groups in cage because of social animal. A large number of papers have previously reported that housing conditions affect behavior, physiology and neurochemistry in laboratory rodents. However, effect of housing conditions on voluntary exercise is not well understood due to a technical problem. In this study, using recent radio frequency identification technology, we investigated the effect of housing conditions on voluntary exercise in laboratory rats. Male Wistar rats were implanted with microchips subcutaneously providing each animal with a unique identification number. Animals were single or group-housed in plastic cages with a running wheel for 4 weeks. Each cage was equipped to monitor an individual animal's access to running wheel using original microchip-scale system. Daily wheel revolutions in each cage were recorded digitally from counters attached to the running wheel, and individual running distance estimated to be calculated by multiplying wheel circumference by the number of revolutions based sequential data of individual access behavior. The result showed no significant difference in average of daily running distance between housing conditions. In group-housed rats, coefficient variation in average of daily running distance was less than 50% but that in single-housed rats was more than 90%. Additionally, there was not significant difference in average of daily running time between housing conditions although we frequently observed not only voluntary running but also playing with cage mates in group housing condition. Furthermore, we focused on alteration of brain monoamine (dopamine, serotonin, and these metabolites) levels which play a crucial role in psychological outcomes and analyzed by high performance liquid chromatography. Two way (housing condition × running condition) ANOVA showed main effects in several brain regions

but no interaction. These results indicated that housing conditions influence characteristic of voluntary exercise and each housing and running condition alters brain monoamine levels respectively, suggesting that housing condition might alter potential brain monoamine levels.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 067.04/PP17

Topic: F.04. Stress and the Brain

Support: CIHR Grant MOP-136840

Title: Sex differences in dorsal raphe nucleus transcriptome responses associated with stress HPA axis habituation

Authors: *T. J. PHILIPPE¹, M. DORDEVIC¹, P. PAVLIDIS², M. UNDERHILL¹, V. VIAU¹
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Abstract: Few studies have explored sex differences in stress hypothalamic pituitary-adrenal (HPA) axis habituation, defined as a reduction in glucocorticoid steroid hormone responses to the same stimulus repeated in a predictable manner. This process is thought to protect the organism against stress-related illness, as sustained elevations in HPA axis activity and glucocorticoid exposure have been linked to increased risk for psychiatric disorders. Here we compared the capacity of adult male and female Sprague-Dawley rats to show adaptive neuroendocrine responses during repeated restraint stress, in addition to changes in transcriptome profiles in the dorsal raphe nucleus (DRN), a key source for serotonin (5-HT) outflow in the brain implicated in stress controllability. Male and females displayed similar declines in HPA output (ACTH, corticosterone) responses between the first and 5th day of 2h restraint exposure. However, analysis of DRN using RNA sequencing across stress naïve, acute and repeat conditions revealed distinct patterns of stress-induced changes in gene transcription that were unique to each sex. As illustrated for the 5-HT system, only males showed changes in the expression of genes associated with 5-HT signal transduction, i.e. 5-HT 1D and 2C receptors, whereas gene responses in females were biased towards those centered on 5-HT metabolism, including tryptophan hydroxylase (TPH 1 and TPH 2) and monoamine oxidase (MAO-A and MAO-B). These results suggest that despite showing comparable capacities for neuroendocrine habituation, this process may be met by different underlying mechanisms of 5-HT control in males and females. We are currently making similar inroads on other systems of interest within the DRN, as well as within various forebrain regions that are targeted by 5-HT and mediating adaptive HPA axis and behavioral responses to stress.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.05/PP18

Topic: F.04. Stress and the Brain

Support: CONACYT Grant 256882

Title: Chronic restraint stress induced increase serotonin transporter expression in rat left adrenal gland

Authors: SHIVSHANKER¹, N. SAROJ², S. MORENO MARTÍNEZ², J. TERRÓN SIERRA², P. LÓPEZ SÁNCHEZ³

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Abstract: Chronic restraint stress (CRS) induced 5-HT transporter expression in rat left adrenal gland due to a mechanism involving increased levels of serotonin (5-HT) in the adrenal glands. Chronic stress increases expression of the 5-HT transporter (5-HTT) in the central nervous system, which removes serotonin released into the synaptic cleft. 5HTT is an important therapeutic target for the treatment of stress-related disorders, including major depression. However, stress leads to activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, which induces increase in systemic adrenocorticotrophic hormone (ACTH) and excessive secretion and effects of the major mediators of the stress response, including corticotropin-releasing hormone (CRH) and glucocorticoids (Chrousos and Gold, 1992) from the adrenal cortex (cortisol in humans, corticosterone in rodents) (Munck and Guyre et al., 1986) as well as from adrenal medulla, respectively. Furthermore, evidence suggests that long time of HPA axis activation has been involved in the pathogenesis of depression and psychiatric conditions in humans (Holsboer F.,2001). It has also been shown that HPA axis dysfunction and 5-HT neurotransmission dysfunction have also been involved in the pathogenesis of major depression. Moreover, chronic restraint stress (CRS) involved acute stress-induced corticosterone secretion in rats through a mechanism involving increased levels of serotonin (5-HT) in the adrenal glands (García-Iglesias et al., 2013). The purpose of the present study is to investigate the effect of CRS (20 min/day as compared to control (CTRL) home cage conditions for 14 days) on 5-HTT-like immunoreactivity (5-HTT-LI) and protein levels in rat whole adrenal glands by western blotting. As it has been reported before, CRS decreased body weight gain and relative thymus weight although, increasing relative adrenals weight. Furthermore, CRS markedly increases 5-HTT-LI

in the left adrenal cortex as well as the 5-HTT expression as suggested by the increased amount of proteins in whole left adrenal gland from CRS as compared to CTRL animals. Together, these results suggest that CRS animals undergo increased serotonergic activity in adrenal glands, which may be linked to increased expression of 5-HTT.

Disclosures: **Shivshanker:** None. **N. Saroj:** None. **S. Moreno Martínez:** None. **J. Terrón Sierra:** None. **P. López Sánchez:** None.

Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

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Topic: F.04. Stress and the Brain

Support: CONACYT grant 256882

Title: Effect of tryptophan hydroxylase inhibition on chronic restraint stress induced changes in 5-HT in adrenal gland of rats

Authors: ***N. SAROJ**¹, .. **SHIVSHANKER**², **S. MORENO MARTÍNEZ**¹, **E. VERA AGUILAR**¹, **J. TERRÓN SIERRA**¹

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Abstract: Chronic stress is one of the key factors predisposing to endocrine disruption in stress-related disorders. Chronic restraint stress (CRS) has been shown to magnify stress-induced corticosterone (CORT) secretion in rats apparently through an ACTH independent mechanism involving increased levels of serotonin (5-HT) in the adrenals glands, particularly in adrenocortical cells (García-Iglesias et al., 2013). In the present study we analyzed the effect of tryptophan hydroxylase (TPH) inhibition with p-chlorophenylalanine (PCPA) on 5-HT levels and TPH protein content as measured by HPLC and Western blot. Male wistar rats were exposed to CRS (20 min/per day, for 14 days) or home cage. On day 15 animals were decapitated for collection of tissue samples. PCPA pretreatment decreased CRS-induced augmentation of 5-HT levels and TPH protein in adrenal glands. These observations support the notion that the increase of adrenocortical 5-HT levels induced by CRS might be accounted for increased synthesis through TPH, the expression of which increases in this tissue.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.07/PP20

Topic: F.04. Stress and the Brain

Support: DA09082

Title: Ultrastructural localization of serotonergic 5-HT_{2A} receptors in the rat locus coeruleus

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Abstract: Stress activates the serotonergic system leading to anxiogenic or anxiolytic behavioral responses depending on the type of serotonin receptor involved. For example, previous studies have shown that serotonergic innervation of the amygdala and hippocampus mediates the anxiogenic effects of serotonin by activating 5-hydroxytryptamine _{2A} (5HT_{2A}) receptors. Pharmacological evidence has shown that serotonin and post-synaptic serotonergic receptors are present in the locus coeruleus (LC), the main noradrenergic nucleus in the brain. While several studies suggest a functional role of 5HT_{2A} in the LC, the anatomical localization of 5HT_{2A} receptors in this nucleus has not been characterized. In the present study, we investigated the cellular sites for interactions between serotonin, 5HT_{2A} receptors and noradrenergic neurons in the LC using immunofluorescence and immunoelectron microscopy. Tissue sections were collected through the LC and processed for immunocytochemical detection of dopamine-β-hydroxylase (DβH), a marker for noradrenergic neurons, 5HT, a marker for serotonin, and 5HT_{2A} receptor. Immunofluorescence microscopy revealed that DβH-containing perikarya and somatodendritic processes exhibited 5HT_{2A} immunoreactivity and were directly apposed by 5HT-containing fibers. Ultrastructural analysis, using immunoperoxidase labeling for DβH and immunogold-silver labeling for 5HT_{2A} further confirmed that 5HT_{2A} are localized within DβH-containing somatodendritic processes. Taken together, these results provide neuroanatomical evidence for direct interactions between the noradrenergic and serotonergic systems in the LC.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

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Topic: F.04. Stress and the Brain

Support: DA09082

Title: Chronic morphine exposure alters the female rat estrous cycle and stress-related peptidergic receptor expression in the locus coeruleus

Authors: *B. A. REYES¹, I. HORRILLO², E. J. VAN BOCKSTAELE³

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Abstract: A variety of drugs, including opioids, cocaine, heroin, antipsychotic and antidepressant medications, have been shown to alter endocrine function in women. Proposed mechanisms of action involve inhibitory influences on gonadotropin secretion that contribute to menstrual cycle dysregulation in women. In addition, the human menstrual and rat estrous cycle have been shown to be dysregulated by exposure to stress. Opioids and the stress-related neuropeptide, corticotropin-releasing factor (CRF) reciprocally regulate the locus coeruleus (LC), a noradrenergic nucleus with broadly projecting efferents within the brain. We have shown that stress regulates CRF receptor (CRFr) expression and distribution in the LC. While most studies in animals have focused on the influence of the estrous cycle on the effect of opioids, few studies have elucidated the effect of opioids on the estrous cycle in normal cycling female rats. Here, we investigated the effects of chronic morphine on estrous cyclicity of normal cycling rats. We measured protein expression of the estrogen receptor α (ER α) and CRFr in the LC. Female Sprague Dawley rats were implanted with morphine for 7 days. Estrous cycle was determined via vaginal cytology. Rats were euthanized, and brains, ovaries and adrenal glands were harvested and dissected. Body weights were obtained at the onset of morphine implantation and during the entire experimental period. Consistent with previous reports, there was a significant decrease in body weight in morphine-implanted rats ($p < 0.01$) compared to placebo-implanted rats. While the weight of adrenal glands/body weight ratio was similar across groups, the weight of the ovaries was significantly decreased ($p < 0.05$) in morphine-implanted rats compared to placebo-implanted rats. Interestingly, morphine caused a prolongation of the estrous cycle ($p < 0.05$) where the diestrus phase was lengthened compared to placebo-implanted rats. In these same subjects, Western blot analysis showed that ER α and CRFr expression levels were significantly decreased ($p < 0.05$) compared to placebo-implanted rats. The results show that

chronic morphine alters the estrous cycle of normal cycling females and disturbs the expression of ER α and CRFr in the LC.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

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Topic: F.04. Stress and the Brain

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Title: Dissecting whole-brain direct connectomic LC-NE network

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Abstract: It is known that norepinephrine (NE) system, primarily originated from the locus coeruleus (LC), plays central roles in arousal, attention, sleep, stress response, and cognition. LC-NE neurons receive inputs from and send outputs to different regions throughout the CNS. However, the characteristics of the connectomic LC-NE network across the whole brain, especially the accurate locations and the types of the pre- and post-synaptic neurons, are not fully understood. For the purpose of mapping out the quantitative panorama of LC-NE neurons' direct input and output networks, newly developed cell-type-specific anterograde mono-synaptic tracer (H129- Δ TK-LSL-tdT), and classic tracer RV, along with helper AAVs, were separately injected into the unilateral LC of DBH-cre mice. After tissue fixing and sectioning, IHC staining, fluorescence imaging, and data analysis, we found that the direct output targets of LC-NE neurons are (1) on both ipsi- and contra-lateral sides, although more on the former; (2) located more in subcortical areas than in the cortex; (3) include both pyramidal neurons and

interneurons; and (4) can reach as far as the sacral spinal cord. Combined with RV tracing of the direct input networks, we found that relative to the LC-NE neurons, a brain region can be input only, output only, or both. Among these areas, the midbrain especially its motor related areas are the most heavily targeted. Compared to projection mapping using AAV-mediated GFP expression, the majority of brain areas identified by the anterograde tracing matches those previous results. Meanwhile, there are several exceptions where an area identified by AAV but not seen in HSV tracing. Further studies are required to clarify these differences raised from different tracers.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

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Title: Genetic identification of a noradrenergic population implicated in alleviation of stress-related responses

Authors: ***Y.-W. CHEN**¹, M. DAS², E. A. OYARZABAL², Q. CHENG¹, N. W. PLUMMER¹, K. G. SMITH¹, G. K. JONES¹, D. MALAWSKY¹, J. L. YAKEL¹, Y.-Y. I. SHIH², P. JENSEN¹
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Abstract: Norepinephrine (NE) has long been regarded as a stress neurotransmitter that can induce anxiety and other stress-related responses. However, this idea is derived primarily from research focusing on the locus coeruleus (LC) noradrenergic system. The functional roles of other central noradrenergic neurons are less well known, due in part to the technical challenge of targeting these loosely-organized cells. Here, using an intersectional chemogenetic strategy in combination with behavioral and physiological analyses, we identified a subpopulation of NE neurons with a unique role in reducing acute stress responses. These neurons share developmental expression of *Hoxb1* (*Hoxb1*-NE neurons) and are scattered throughout the

subcoeruleus, A5, A2, and A1 noradrenergic nuclei. Similar to the LC, this population provides substantial input to multiple forebrain regions implicated in stress regulation. We found that chemoactivation of *Hoxb1*-NE neurons promotes a more active coping response during forced swim and tail suspension stress, a phenomenon not observed when we selectively stimulate LC neurons. Results from light dark box and elevated plus maze further show that activation of *Hoxb1*-NE neurons lead to an anxiolytic response, which was no longer present with pre-administration of adrenergic antagonists. This result stands in sharp contrast to the increased anxiety-like behavior following LC stimulation. We also found that activation of *Hoxb1*-NE neurons markedly reduces heart rate, suggesting that these neurons may mediate physiological aspects of the stress response. Consistent with these phenotypes, results from functional magnetic resonance imaging and Fos immunohistochemistry reveal reduced neuronal activity across multiple stress-related regions—including the bed nucleus of the stria terminalis, amygdala, and LC—upon activation of *Hoxb1*-NE neurons. Our results indicate that contrary to the general belief that the NE system facilitates the stress response, activation of *Hoxb1*-NE neurons alleviates the emotional and physiological manifestation of stress. These findings clearly demonstrate that the NE system consists of multiple functional subpopulations and argue for caution when interpreting results from manipulation of the entire NE system.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.11/QQ2

Topic: F.04. Stress and the Brain

Support: NIH Grant MH106757

Title: VTA GABA neurons mediate sex-specific susceptibility to subchronic variable stress

Authors: **B. THOMPSON**, C. BOUARAB, M. DIMOLA, *A. M. POLTER
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Abstract: Women are roughly twice as likely as men to be diagnosed with a mood or anxiety disorder. Given that stress plays a significant role in the development of mood and anxiety disorders, sexual dimorphisms in the response to stress are likely to be a critical factor in the enhanced vulnerability of females to these disorders. Across both human populations and animal models, males and females exhibit divergent responses to stress at all levels, from molecular signatures to behavioral adaptations. Subchronic variable stress (SCVS) is a model of depression

and anxiety in which female mice develop anhedonia and anxiety but males do not (LaPlant et al, *Biological Psychiatry*, 2009; Hodes et al, *J. Neuroscience*, 2015). In this study, we use this model to investigate the role of VTA GABA neurons in sex differences in the response to stress. Dysregulation of the mesolimbic reward circuitry is implicated in the pathophysiology of stress-related illnesses such as depression and anxiety. VTA GABAergic neurons are poised to be a critical node in the regulation of female-specific maladaptive behavior following SCVS. These neurons regulate activity of the mesolimbic dopaminergic pathway, both by gating the activity of neighboring dopamine neurons and through a projection to the NAc. In addition, VTA GABA neurons also project to the ventral pallidum and the lateral habenula, brain regions highly implicated in depressive-like behaviors. VTA GABA neurons modulate reward and anxiety-related behaviors and are activated by acute stressors; however, little is known about neuroadaptations in these neurons in response to chronic or repeated stressors. We hypothesize that SCVS increases activity of GABAergic neurons in the VTA in female animals, and that reversing this will decrease SCVS-induced behavioral deficits.

Here, we use a chemogenetic approach to investigate this hypothesis. We find that inhibition of VTA GABAergic neurons decreases anxiety-like behavior in female mice following SCVS. In contrast, inhibition of VTA GABAergic neurons had no effect on anxiety in unstressed females, or in males. In parallel, we are using whole-cell electrophysiology to investigate excitability and synaptic function of VTA GABAergic and dopaminergic neurons in male and female animals following SCVS. Our data indicate a significant role for VTA GABA neurons in mediating female-specific susceptibility to stress and suggest that regulation of the VTA microcircuitry in response to stress may be sexually dimorphic.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.12/QQ3

Topic: F.03. Neuroendocrine Processes

Support: T32 Grant NS077413
DARPA Grant W911NF1010093

Title: Molecular and circuit mechanisms underlying paraventricular thalamic regulation of habituation to stress

Authors: *B. CORBETT, S. LUZ, A. CURTIS, J. ARNER, S. BHATNAGAR
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Abstract: Disrupted habituation is a signature of PTSD, causing devastating effects for those afflicted. Understanding the molecular and neural substrates underlying habituation may allow for improved therapies for PTSD patients. In rats, we model habituation using the repeated restraint paradigm. Exposure to this moderately intense stressor increases the expression of immediate early genes in certain brain regions, induces the production of stress-related hormones, and elicits struggle behavior. All of these responses are highest on day 1 of restraint and attenuate by the 5th to 7th exposure. We have previously identified the posterior paraventricular thalamic nucleus (pPVT) as a crucial brain region that regulates habituation. Using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), we investigated the role of the pPVT in regulating the stress response. Compared to controls, chemogenetic inhibition of the pPVT increased adrenocorticotrophic hormone (ACTH) on day 1 and attenuated habituation as ACTH and corticosterone remained elevated on the 5th day of restraint. We observed coherent network activity between the pPVT and medial prefrontal cortex (mPFC), which regulates negative feedback of the stress response. We found that chemogenetic inhibition of a subset of pPVT neurons that project to the mPFC was sufficient to attenuate habituation of struggle behavior. We hypothesize that pPVT neurons, in particular those that project to the mPFC, play a critical role in stress habituation. Furthermore, we investigated whether pPVT Arc regulated habituation. Arc is an immediate early gene that mediates neuronal plasticity and dendritic spine subtype densities. We found that pPVT Arc was increased on day 1, but not day 5, of restraint in naïve rats. Furthermore, Arc knockdown in the pPVT attenuated habituation. Preliminary data showed that numbers of mushroom spines are specifically increased by repeated restraint in male rats and that complexity of dendritic spines is altered by stress in male rats. Our findings offer new insight into the role of the pPVT in mediating the stress response and are among the first to provide potential molecular and network mechanisms of stress habituation.

Disclosures: **B. Corbett:** None. **S. Luz:** None. **A. Curtis:** None. **J. Arner:** None. **S. Bhatnagar:** None.

Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.13/QQ4

Topic: F.04. Stress and the Brain

Support: NSF-GRFP

Title: Stress-modulated learning in eyelid conditioning

Authors: *C. BLEVINS¹, R. A. GRAY², B. V. ZEMELMAN³

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Abstract: Heightened stress response and elevated levels of stress-related neuropeptides such as corticotropin-releasing factor (CRF) are common features of neuropsychiatric disorders including anxiety, depression, and post-traumatic stress disorder. Here, we use classical eyelid conditioning to examine learning in two mouse models that exhibit a heightened stress response, the triple-transgenic (3xTg) model and the social isolation stress model. We observe more rapid acquisition and higher levels of conditioned responses in both 3xTg and isolation stress models compared to non-stressed, non-transgenic controls. Interestingly, both models also exhibit response timing deficits during two-cue discrimination conditioning, wherein animals are simultaneously trained in delay conditioning with a 250 ms inter-stimulus interval (ISI), and delay 400 ms ISI to counterbalanced light and tone cues. Unstressed, non-transgenic mice learn to discriminate cues and produce two differently-timed responses, while stressed and 3xTg mice learn the task with more difficulty, more often producing responses with incorrect timing. In addition to its role in the limbic system, CRF also enhances cerebellar learning via input from the inferior olive. To get an idea of how limbic versus olivo-cerebellar CRF circuits may be differentially involved in eyelid conditioning, we correlate behavioral outcomes with c-Fos protein and CRF mRNA measurements in these regions. Behavioral results described here suggest that stress modulation in the cerebellar system may be driving both enhanced learning and poor cue discrimination, perhaps by increasing the efficacy of climbing fiber signals through an increase in inferior olive CRF.

Disclosures: C. Blevins: None. R.A. Gray: None. B.V. Zemelman: None.

Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.14/QQ5

Topic: F.04. Stress and the Brain

Support: the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research JP16K01603
2016 Tokai University School of Medicine Research Aid

Title: Inhibition of PVN neurons influences stress-induced changes of motor learning in the VOR

Authors: *A. KATO¹, A. YAMAGIWA²

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Abstract: Under stressful conditions, the endocrine system is activated through the stress-related responses in the brain, resulting in a variety of changes in the physiological status and behavior. It is known that motor learning-induced behavioral changes are potentially influenced by the stress-exposure, e.g. performance of athletes, however, molecular and circuit-level mechanisms in the brain for the relationship between motor learning and stress are not clear. Here we empirically examined the influence of a couple of different stresses to adaptive changes in the vestibulo-ocular reflex (VOR) in male mice. First, we found the concentration of the corticosterone, a glucocorticoid as an index of stress-exposure, increased in urine sampled every 90 min after head/body-restrained or co-housing with another non-littermate male mouse. We also found significantly less amount of learned increases in the VOR when the given visual stimuli combined with the vestibular stimuli for training started after 90 min of restrained or co-housing stress. Using the gene manipulated mice expressing the archaerhodopsin T (ArchT) selectively on the corticotropine releasing factor (CRF)-positive cells, we illuminated their brain region around the paraventricular nucleus (PVN) with 525 nm LED (Teleopto, Bio Research Center, Japan) through the stereotaxically implanted cannula to inactivate CRF-positive neurons in the PVN during the last 30 min of 90 min of restrained stress and during whole 30 min training stimuli for the increase of the VOR, and found significant adaptive changes in the VOR. Taken together with our previous report in the SfN that CRF local administration to the cerebellum enhanced cerebellum-dependent motor learning, our current results suggest differential roles of CRF in the PVN and the cerebellum for motor learning under stress exposure.

Disclosures: A. Katoh: None. A. Yamagiwa: None.

Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.15/QQ6

Topic: F.04. Stress and the Brain

Support: NSF IOS #1656734

Title: Influence of categorically distinct stressors on visual attention to food in humans

Authors: S. LI¹, J. R. KEENE², B. N. HARRIS¹, *J. A. CARR³

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Abstract: Neuroanatomical, biochemical, and physiological studies support the idea of two (or more) pathways relaying stressor information to CRF neurons in the paraventricular nucleus (PVN); anticipatory stressors that reach the PVN through limbic system pathways and so-called reactive stressors that ascend from the brainstem via ventral noradrenergic pathways. While both anticipatory and reactive stressors have been reported to modulate food intake, there has been little work comparing anticipatory and reactive stressor influences on eating behavior in humans. We examined the influence of an anticipatory stressor (Trier-social stress test, TSST) and a reactive stressor (cold-pressor test, CPT) on visual attention to food images in human participants. Sixty participants were divided equally between control, TSST, or CPT groups. We measured salivary cortisol levels before and after stressor exposure to gauge activity of the HPA axis. Following stressor exposure participants carried out an eye-tracking test (5 replicates per participant, averaged) using a standardized food picture database (Food-pics; Bleichert et al., 2014). We analyzed three metrics in balanced pairs of food and non-food images: saccade latency, gaze duration, and saccade bouts. Salivary cortisol was elevated over baseline in both stressor groups. Preliminary ANOVA analysis of stressor treatment (between groups) and image type (within groups) with harmonic mean replacement of missing data revealed no statistically significant main or interaction effects of the stressors on any of the three eye movement variables. We did find a statistically marginal trend for CPT reducing ($p=0.07$ main effect, post-hoc $p=0.03$ for CPT relative to control) gaze duration on food images with our preliminary ANOVA analysis, suggesting this variable may be biologically relevant. There was a main effect of image type within each treatment, with participants spending more time looking at food images across all treatment groups. Thus far, analyses suggest both stressors types were effective (as determined by elevated salivary cortisol), that food images are viewed more intently than non-food images, and that neither anticipatory or reactive stressor exposure robustly affect the visual attention to food images.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.16/QQ7

Topic: F.04. Stress and the Brain

Support: Rowan University School of Osteopathic Medicine startup funds

Title: Behavioral susceptibility to acute stress is associated with decreased opioid receptor expression in the locus coeruleus

Authors: T. LOVEGROVE, O. BORODOVITSYNA, *D. J. CHANDLER
Cell Biol. and Neurosci., Rowan Univ. Sch. of Osteo. Med., Stratford, NJ

Abstract: Stress is a series of physiological and behavioral responses to harmful or threatening stimuli that are centrally orchestrated by a number of circuits, including the brainstem nucleus locus coeruleus (LC). Stress causes release of corticotropin releasing factor (CRF) in LC, increasing its discharge, elevating forebrain levels of norepinephrine (NE), and promoting hypervigilance and anxiety-like behavior. Upon stressor termination, endogenous opioids are released in LC to limit its activity and potentially facilitate a return to a non-anxious behavioral state. Recently we have shown that exposure to an intense acute stressor, simultaneous physical restraint and predator odor exposure (RST+TMT), causes robust increases in anxiety-like behavior that persist for at least a week and are accompanied by increased LC discharge and excitability. To investigate potential mechanisms for persistent LC hyperactivity, we used RT-PCR to quantify relative expression levels of CRF, μ -opioid (MOR) and δ -opioid (DOR) receptor genes in LC tissue punches from control and stressed rats. While *crhr1* expression was unaffected by stress, *oprm1* and *oprd1* were both significantly decreased in the stress group. To determine if less intense stressors would not as robustly affect gene expression or behavior, we exposed additional cohorts of rats to restraint only (RST) or predator odor only (TMT), and a week later assayed anxiety-like behavior in the open field test. Rats were then sacrificed and their brains prepared for RT-PCR. Using principal components analysis, we found that rats exposed to RST or TMT segregated into two non-overlapping distributions: a susceptible group whose behavior closely matches that of rats exposed to RST+TMT, and a resilient group whose behavior is similar to controls. Furthermore, when gene expression was quantified according to this convention, stress resilient rats showed expression levels of *oprm1* and *oprd1* similar to controls, while these genes were downregulated in the susceptible group to levels similar to those in rats exposed to both stressors. Preliminary electrophysiological results also show that LC neurons from rats exposed to RST+TMT are insensitive to a DOR agonist, suggesting that altered gene expression translates into a functional outcome. These results suggest that while RST+TMT affects LC opioid receptor expression and function in nearly all animals, moderate stress produces these effects only in a subset of susceptible rats. Furthermore, altered opioid receptor expression may contribute to the persistently hyperactive LC we have identified to promote long-lasting increases in anxiety-like behavior.

Disclosures: T. Lovegrove: None. O. Borodovitsyna: None. D.J. Chandler: None.

Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 067.17/QQ8

Topic: F.04. Stress and the Brain

Support: Rowan University school of osteopathic medicine startup funds

Title: Age- and stress-dependent changes in locus coeruleus physiology and anxiety-like behavior

Authors: *O. BORODOVITSYNA, D. J. CHANDLER
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Abstract: Adolescence is characterized by increased sensitivity toward psychological stressors. The locus coeruleus (LC) is the main source of norepinephrine (NE) in the central nervous system and plays a major role in the stress response. Activation of LC by corticotropin releasing factor causes release of NE in the forebrain and modulates behavior and arousal. We have previously shown that a single stressful episode in adolescent rats produces long-lasting anxiety-like behavior and electrophysiological changes in LC. We hypothesized that the same acute stressor would cause different behavioral and physiological responses in adult and adolescent rats both immediately and one week after stressor exposure. Mid-adult (77PND) and mid-adolescent animals (42PND) were exposed to 15 minutes of combined predator odor and restraint stress. Anxiety-like behavior and LC electrophysiological properties were assessed immediately after or one week after stressor exposure. Additionally, to assess the endocrine branch of the stress response, serum was collected immediately prior to, 35 minutes after, and a week after stressor exposure. Immediately after stress, both adult and adolescent rats demonstrated increased anxiety-like behavior, an effect which persisted for one week in the adolescent, but not adult rats. Interestingly, although adult rats showed less anxiety-like behavior a week after stressor exposure than adolescents, they demonstrated a greater increase in serum corticosterone levels compared to adolescents. LC neuronal resting membrane potential and threshold which were both increased in adult rats regardless of treatment, suggesting that the physiological properties of LC neurons change along the normal developmental trajectory. There was also a main effect of stressor exposure on cell excitability, as indicated by increased spontaneous firing rate and input resistance in both age groups. Taken together, these results show that acute stressor exposure alters the electrophysiological properties of adolescent as well as adult LC neurons at both immediate and long-term time points, but these effects are less dramatic in adult animals. Behaviorally, adult rats demonstrated stress resilience compared to adolescent rats one week after stressor exposure, and had higher corticosterone levels in response to stressor exposure. These findings show that while LC neurons are sensitive to stressor exposure during both adolescence and adulthood, the effect of stress on anxiety-like behavior is blunted in adulthood. This could suggest that LC might have a less critical role in mediating anxiety-like behavior in adult than adolescent animals.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.18/QQ9

Topic: F.04. Stress and the Brain

Support: NIGMS GM63904

NIDDK DK84567

NIDA DA032194

Title: Locomotor response to acute stressors requires hypothalamic-pituitary-interrenal axis activation and glucocorticoid receptor

Authors: *H. LEE¹, T. L. SCHWAB², A. N. SIGAFOOS², J. L. GAUERKE³, R. G. KRUG, II², M. R. SERRES², D. C. JACOBS⁴, R. P. COTTER², B. DAS⁵, M. O. PETERSEN⁶, C. L. DABY², R. M. URBAN⁷, B. C. BERRY⁸, K. J. CLARK¹

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Abstract: When vertebrates face acute stressors, their bodies rapidly undergo a repertoire of physiological and behavioral adaptations, which is termed the stress response (SR). Rapid physiological changes in heart rate and blood sugar levels occur via the interaction of glucocorticoids and their cognate receptors following hypothalamic-pituitary-adrenal (HPA) axis activation. These physiological changes are observed within minutes of encountering a stressor and the rapid time domain rules out genomic responses that require gene expression changes. Although behavioral changes corresponding to physiological changes are commonly observed, it is not clearly understood to what extent HPA axis activation dictates adaptive behavior. We hypothesized that rapid locomotor response to acute stressors in zebrafish requires HPI axis activation. In teleost fish, interrenal cells (I) are functionally homologous to the adrenal gland cortical layer. We derived 8 frameshift mutants in genes involved in HPI axis function: two mutants in exon 2 of *mc2r* (adrenocorticotrophic hormone receptor), two in each of exon 2 and exon 5 of *nr3c1* (glucocorticoid receptor), and two in exon 2 of *nr3c2* (mineralocorticoid receptor). Exposing larval zebrafish to mild environmental stressors, acute changes in salinity or light illumination, results in a rapid locomotor response. We show here that this locomotor response requires a functioning HPI axis via the action of *mc2r* (adrenocorticotrophic hormone receptor) and the canonical glucocorticoid receptor encoded by *nr3c1* gene, but not mineralocorticoid receptor (*nr3c2*). Our rapid behavioral assay paradigm based on HPI axis

biology may prove useful to screen for genetic, pharmacological, or environmental modifiers of the HPA axis.

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Poster

067. Stress-Modulated Pathways, Neuromodulators, and Behavior

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 067.19/QQ10

Topic: F.04. Stress and the Brain

Support: NIH MH101178

Seed funds from Rowan University

Title: Neurochemical and electrophysiological characterization of target-specific neuronal populations in the rat dorsal raphe nucleus and their susceptibility to chronic CORT administration as a model of depression

Authors: E. PROUTY¹, D. CHANDLER², W.-J. GAO¹, *B. D. WATERHOUSE²

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Abstract: Serotonin (5-HT) neurons in the dorsal raphe (DR) nucleus project throughout the forebrain and are implicated in many homeostatic physiological processes and neuropsychiatric disorders. Heterogeneity among DR 5-HT neurons with respect to their anatomical relationships, neurochemical profiles, and electrophysiological properties is well-recognized, but only recently have studies begun aligning such phenotypic variations with specific brain functions. The goal of this work was to link DR neurons to the operation of cognitive and emotional circuitry or sensory processing networks by characterizing cells according to their neurotransmitter expression, electrophysiological profiles, and efferent connectivity; specifically, neurons projecting to the medial prefrontal cortex (mPFC, a region involved in cognition and mood regulation) or the lateral geniculate nucleus (LGN), a visual sensory relay. A further goal was to determine whether serotonergic regulation of cognitive/emotional function might be selectively impacted by a glucocorticoid-excess model of rodent depression; therefore, we examined the effect of chronic corticosterone (CORT) administration on the electrophysiology of these target-specific neuronal populations. Following retrograde tracer injection in mPFC or LGN (and once-daily injections of CORT at 40 mg/kg S.C. for 21 days in a subset of animals), rat brainstem sections containing the DR were immunohistochemically stained for 5-HT and co-transmitters or used for whole-cell

patch clamp recordings. We found that neuronal nitric oxide synthase was expressed in a significantly greater proportion of neurons projecting to mPFC than to LGN (60% vs 22%)—a neurochemical bias consistent with the emerging role of nitric oxide in stress responses and depression. Additionally, only mPFC-projecting neurons displayed CORT-induced hypo-excitability, suggesting that protracted exposure to excess glucocorticoids may preferentially reduce 5-HT output in the mPFC. In summary, these data indicate that subsets of DR 5-HT neurons, defined by efferent connectivity and co-transmitter expression, respond selectively to elevated CORT levels and may account for functionally-specific differences in 5-HT transmission under normal conditions and in neuropsychiatric disease states. Based upon these initial findings we propose that the observed hypo-excitability in DR-mPFC projecting cells may underlie the cognitive deficits and emotional disturbances characteristic of depression and that functional enhancement of 5-HT neurotransmission may correlate with the positive therapeutic responses to serotonergic antidepressants.

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Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.01/QQ11

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15K07140)
Yamada Research Grant

Title: Royal jelly ameliorates diet-induced obesity and glucose intolerance by promoting brown adipose tissue thermogenesis in mice

Authors: *A. TERAO¹, T. YONESHIRO², R. KAEDE², K. NAGAYA², J. AOYAMA², M. SAITO², Y. OKAMATSU-OGURA², K. KIMURA²

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Abstract: Background: The anti-obesity effects of royal jelly (RJ) and bee larva (BL) remain elusive and the mechanisms are unknown. Objective: The aim was to investigate the impact of the dietary supplementation with RJ and BL on energy balance, glucose homeostasis, hepatic steatosis, and thermogenic capacities of brown (BAT) and white adipose tissue (WAT) in mice. Methods: Male C57BL/6J mice were fed with four different experimental conditions for 17 weeks: normal diet (ND), high fat diet (HFD), HFD with 5% RJ, and HFD with 5% BL. Food intake, spontaneous locomotor activity, body composition, hepatic triglyceride (TG) content, and

blood parameters were examined. Insulin sensitivity was assessed from homeostasis model assessment-insulin resistance (HOMA-IR). Gene and protein expressions of the key thermogenic molecule in BAT and WAT were investigated by quantitative real-time PCR and Western blotting analysis, respectively. Results: Although the BL treatment had no effect on diet-induced obese phenotypes, dietary RJ suppressed the HFD-induced increases in body and WAT weights, plasma glucose and insulin, and non-esterified fatty acid. The RJ mice exhibited decreased HOMA-IR and hepatic TG content. These RJ effects were independent of energy intake and locomotor activities. Uncoupling protein 1 (Ucp1) mRNA level in BAT was significantly higher in the RJ group than in the ND group, although the HFD and BL groups differed negligibly from the ND group. Moreover, dietary RJ, but not BL, resulted in a parallel increase in UCP1 and cytochrome c oxidase subunit IV (COX-IV) protein contents in BAT, indicating that RJ synergistically promotes BAT thermogenic capacities by UCP1 induction and mitochondrial biogenesis. Neither the RJ nor BL treatment induced browning of WAT. Conclusions: Dietary RJ supplementation elevates BAT thermogenesis and thereby ameliorates diet-induced obesity, glucose intolerance, and hepatic steatosis. RJ may be a novel promising food ingredient to combat obesity and related metabolic disorders.

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Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

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Program #/Poster #: 068.02/QQ12

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Intramural Research Program of the NIH

Title: Impact of sex differences on the metabolic and neurological effects of chronic caffeine administration in mice

Authors: *S. CAMANDOLA¹, E. MURPHY¹, R. CUTLER¹, J. FIORI O'CONNELL², M. P. MATTSON¹, N. PLICK¹

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Abstract: For centuries caffeine, mostly in the form of coffee and tea, has been used as an endurance and cognitive stimulant. The acute effects of caffeine on arousal, locomotion, metabolism, and cognitive performance are attributed to adenosine receptor antagonism. In the last decade, epidemiological studies have shown that habitual caffeine consumption negatively

correlates with memory decline during normal aging, and with the incidence of various neurodegenerative disorders. The same studies have also begun to unravel gender differences in how chronic caffeine consumption impacts brain health. For example, moderate coffee intake is consistently associated with reduced (24-30%) Parkinson's (PD) incidence in men (Hernan et al., *Ann Neurol* 2002;52:276-284). On the other hand, higher caffeine intake exacerbates the incidence of PD in women under hormonal replacement therapy (Ascherio et al., *Neurology* 2003;60:790-795). While it was shown that estrogen influences caffeine metabolism, the influence of sex on physiological responses to caffeine is still largely unknown. Here we report the results of a study aimed at characterizing the metabolic and neurological responses of male and female mice to chronic caffeine administration. C57Bl/6J of both sexes were kept on *ad libitum* standard NIH diet (carbohydrate: 44.2%; protein: 18%; fats: 6.2%) and water or 0.03% caffeinated water for 8 weeks. Body weight, and food and drink consumption were monitored weekly for the study duration. The Comprehensive Lab Animal Monitoring System was used to determine the overall metabolic changes induced by caffeine. Behavior in open field, elevated plus maze and Y maze was also assessed. Our results show that sex strongly influences the metabolic and behavioral responses to chronic caffeine intake.

Disclosures: **S. Camandola:** None. **E. Murphy:** None. **R. Cutler:** None. **J. Fiori O'Connell:** None. **M.P. Mattson:** None. **N. Plick:** None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.03/QQ13

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Mitchell Center Internal Funds

Title: Adipose tissue-targeted stem cell transplantation for insulin resistance-related CNS dysfunction

Authors: ***S. SAIEVA**^{1,2}, **B. KRISHNAN**¹, **G. LA ROCCA**⁴, **N. ABATE**³, **G. TAGLIALATELA**¹

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Abstract: Type 2 Diabetes Mellitus (T2DM) is a main risk factor for the development of Alzheimer's Disease (AD). Compelling epidemiological evidence demonstrated that AD and insulin resistance (a major pathological feature of T2DM) are linked, although the underlying mechanisms remains uncertain. Insulin resistance has been demonstrated in brain of AD patients,

where it might be prodromal to neurodegeneration. In the CNS, especially in those areas associated with cognitive function such as the hippocampus, insulin plays a key role in promoting memory and learning processes. High-caloric diets may lead to adipose tissue (AT)-insulin resistance, resulting in fatty acid spillover and ectopic fat deposition. Notably, high levels of FFA have been reported in AD patients; likewise, rodents fed with high-fat diets display peripheral insulin resistance, as well as hippocampal synaptic deficiencies with reduced insulin signaling and memory deficits. These observations indicate that AT dysfunction directly impinges on CNS function, thus suggesting that improving peripheral insulin sensitivity may also improve associated memory deficits. Furthermore, the number of mesenchymal stem cells (MSC) within the AT in patients with insulin resistance and T2DM is significantly reduced, which suggests that replenishing deficient MSC in the AT may successfully halt/reverse insulin resistance and its systemic consequences, including CNS deficiencies. With this ultimate goal in mind, we investigated the effect of a transplant of Wharton jelly-derived mesenchymal stem cells (WJ-MSC) directly in AT in restoring insulin sensitivity in both periphery and brain in insulin-resistant high-fat fed wild-type mice. Our results show that after MSC transplantation there is a significant improvement of hyperglycemia, increased synaptic insulin signaling and restored synaptic plasticity as evidenced by recovery of long-term potentiation expression and amelioration of memory function. Collectively, the present data suggest that re-establishing AT insulin sensitivity via peripheral transplantation of MSC could be a viable therapeutic strategy to correct insulin resistance-associated CNS deficits as those normally seen in T2DM and possibly AD.

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Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.04/QQ14

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: HFSP LT 000576/2013.
NIH grant DA036408
NIH grant GM123558

Title: Reshaping circadian metabolism in the suprachiasmatic nucleus and prefrontal cortex by nutritional challenge

Authors: *P. TOGNINI^{1,2}, K. KINOCHI², Y. LIU⁴, J.-C. HELBLING^{2,5}, K. L. ECKEL-MAHAN⁶, P. BALDI³, P. SASSONE-CORSI²

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Abstract: From Cyanobacteria to humans, important aspects of organismal physiology are under the control of a specialized timekeeper called circadian clock. The endogenous clock anticipates daily environmental changes, optimizing physiological processes in order to increase survival rates. Food is a powerful entrainment cue for circadian clocks in peripheral tissues, and changes in the composition of nutrients have been demonstrated to metabolically reprogram peripheral clocks. However, how food challenges may influence circadian metabolism of the master clock in the suprachiasmatic nucleus (SCN) or in other brain areas remains unknown. By using high-throughput metabolomics we explored the circadian metabolome profiles of the SCN and medial prefrontal cortex (mPFC) in comparison with mice challenged with a high-fat diet (HFD). Both mPFC and SCN displayed robust cyclic metabolism with a strikingly high sensitivity to HFD perturbation in an area-specific manner. Phase and amplitude of oscillations were drastically different between SCN and mPFC and the metabolic pathways impacted by HFD were remarkably area-dependent. Furthermore, the circadian reorganization of metabolic pathways was accompanied by correspondent changes in gene expression, suggesting a striking coherence in transcriptome and metabolome oscillation in brain clocks. Finally, HFD induced a significant increase in the number of cycling metabolites exclusively in the SCN, revealing an unsuspected susceptibility of the master clock to food stress.

Disclosures: P. Tognini: None. K. Kinouchi: None. Y. Liu: None. J. Helbling: None. K.L. Eckel-Mahan: None. P. Baldi: None. P. Sassone-Corsi: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.05/QQ15

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Fondazione Enrico ed Enrica Sovena Grant

Title: Selective effects of L-acetylcarnitine on energy-utilizing ATPases of synapses derived from hippocampal sub-fields

Authors: *F. FERRARI, L. BAGINI, A. GORINI, R. F. VILLA
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Abstract: Maintenance of synaptic structure and functionality is a highly energy-dependent process and perturbations of cellular energy metabolism occur during aging [1], neurodegenerative diseases like Dementias [2], and Depression [3]. Thus, the study of synaptic bioenergetics is useful to evaluate new therapeutic targets. L-acetylcarnitine (LAC) influences synaptic transmission increasing mitochondrial O₂ utilization [4] and its clinical efficacy was previously reported in Alzheimer's Disease and Depression [5, 6]. Therefore, the effect of LAC subchronic *in vivo* treatment was evaluated at two doses (30 and 60 mg x kg⁻¹ *i.p.*, 28 days, 5 days/week) on the maximum rate (V_{max}) of the following energy-utilizing enzymatic systems (ATPases): (i) Na⁺, K⁺, Mg²⁺ ATPase; (ii) Na⁺, K⁺ ATPase; (iii) Mg²⁺ ATPase; (iv) Ca²⁺, Mg²⁺ ATPase. Also (v) ATP synthetase and (vi) acetylcholinesterase (AChE) activities were assayed. Catalytic properties of enzymes were assayed on large synaptosomes (LS) obtained from *hippocampus* of single rats (4 month-old females), a vulnerable area to Dementias and Depression. The major changes on ATPase activities were observed at the dose of 60 mg x kg⁻¹: Na⁺, K⁺ ATPase was increased, while Ca²⁺, Mg²⁺ ATPase decreased, being the other ATP-ases unaffected. ATP synthetase activity was increased by LAC at both doses. AChE activity was not modified by LAC, coherently with the fact that LS derive from glutamatergic mossy fibers^[1] connecting granule cells of dentate gyrus with apical^[1] dendrites of CA₃ pyramidal cells [1], showing low AChE activity. Overall, these results are in accordance with those obtained on the same enzymatic parameters evaluated on hippocampal synaptic plasma membrane subfractions [7]. LAC increased energy consumption linked to modulation of resting membrane potential, but decreased that linked to synaptic Ca²⁺ extrusion, not interfering with cholinergic neurotransmission. Because enzyme activities possess different subcellular sensitivity to drugs, in the future these activities will be studied also on small synaptosomes (SS), derived from septo-hippocampal fibers cholinergic nerve endings.^[1] **References:** [1] Villa RF et al. J Proteome Res 2013; 12: 5422-35. [2] Small SA et al. Nat Rev Neurosci 2011; 12: 585-601. [3] Ferrari F & Villa RF. Mol Neurobiol 2017; 54: 4847-65. [4] Gorini A et al. Neurochem Res 1998; 23: 1485-91. [5] Montgomery SA et al. Int Clin Psychopharmacol 2003; 18: 61-71. [6] Koran LM et al. J Clin Psychopharmacol 1995; 15: 421-7. [7] Ferrari F et al. Eur J Pharmacol 2015; 756: 67-74. **Acknowledgements.** This Research was supported by a Grant of “*Enrico ed Enrica Sovena Foundation*”, Rome, for Dr. Ferrari's Fellowship.

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Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.06/QQ16

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH BRAIN Initiative grant R01MH111359

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Title: Long-term optogenetic activation of mouse cortical neurons after cardiac arrest

Authors: *M. THUNEMANN¹, T. V. NESS⁴, K. KILIÇ^{5,2}, H. UHLIROVA⁶, L. F. BARROS⁷, A. M. DALE³, G. T. EINEVOLL⁸, A. DEVOR^{3,9}

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Abstract: Most of the energy used by the brain's gray matter is expended on moving ions against their concentration gradients across neuronal membranes. This process maintains and restores membrane potentials after spiking and synaptic currents. According to standard textbooks, the energy needed for mammalian brain function is produced mostly, if not entirely, via oxidation of glucose to carbon dioxide and water. This notion is also based on observations that spontaneous and evoked cortical neuronal activity (and conscious perception) are lost within ~15 seconds of blood flow interruption, e.g., due to cardiac arrest.

Therefore, we were surprised to discover that cortical neurons in mouse brain continue to restore their membrane potential for up to 20 minutes after cardiac arrest, even when they were repeatedly depolarized via optogenetic stimulation (Figure 1). Oxygen is not transported during this period, suggesting that mammalian neurons have access to sufficient amounts of ATP via other oxygen-independent mechanisms such as glycolysis, which allows them to maintain the operation of ion pumps.

Understanding the mechanisms underlying this phenomenon will provide fundamental knowledge of biomedical importance on brain metabolism, which could impact the current practice of resuscitation, could lead to a better interpretation of noninvasive imaging data, and could provide neuro-energetic insight into what makes us conscious.

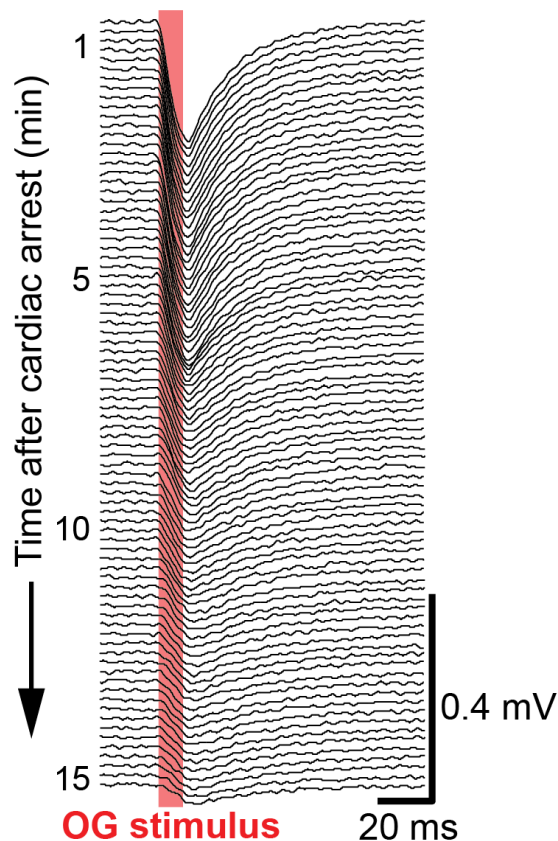


Figure 1. Local field potential response to optogenetic (OG) stimulation (red) in a Thy1-ChR2 mouse. An electrode array was inserted into somatosensory cortex (recording from one out of 23 channels is shown). 450-nm laser light for optogenetic stimulation of Channelrhodopsin-2 (ChR2) was delivered via an optical fiber (10-ms pulses at a frequency of 1 Hz). Cardiac arrest was caused by injection of a sodium pentobarbital overdose.

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Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.07/QQ17

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Tentonin3/TMEM150C contributes to glucose-stimulated insulin release in pancreatic β -cells

Authors: *J. WEE^{1,3}, G. HONG², S. PAK², U. OH²

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Abstract: Impaired insulin secretion and glucose tolerance are key features of type 2 diabetes. Elevation of cytosolic calcium (Ca^{2+}) in pancreatic β -cells is required for exocytosis of insulin granules upon glucose stimulation, which process is known as glucose-stimulated insulin secretion. Ca^{2+} influx is triggered by membrane depolarization, which activates voltage-gated Ca^{2+} channels. Apart from the well known ATP-sensitive K^+ (K_{ATP}) channel-dependent pathway, previous studies predicted the existence of K_{ATP} channel-independent pathway in glucose stimulated insulin secretion. Increased uptake of glucose accelerates glycolysis with accumulation of metabolites, which increases the β -cell volume by osmotic differences. The inflated pancreatic β -cells upon high extracellular glucose level would activate stretch-activated cation channels through which cation influx leads to membrane depolarization of β -cells followed by insulin secretion. Therefore, mechanosensitive channels activated by the stretch of β -cell membrane would be a new therapeutic target for diabetes. Here, we suggest that Tentonin 3 (TTN3), a mechanosensitive cation channel with slow-inactivation kinetics, contributes to the latter pathway. We found high expression of TTN3 in insulin-secreting pancreatic β -cells, where slowly adapting mechanosensitive currents in response to mechanical stimuli were found. Both high glucose and hypotonic solutions induced cationic currents in pancreatic β -cells of wild-type (WT) mice, which were reduced in β -cells of *Ttn3* knock out (KO) mice. In addition, glucose-stimulated insulin secretion *in vitro* or *in vivo* was lower in *Ttn3* KO mice. Taken together, our data indicate that TTN3 contributes to pancreatic β -cell membrane depolarization in response to high glucose and mediates the glucose-stimulated insulin secretion.

Disclosures: J. Wee: None. G. Hong: None. S. Pak: None. U. Oh: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.08/QQ18

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: American Diabetes Association Pathway to Stop Diabetes Grant 1-15-INI-12

Title: Characterization of olfactory circuits modulating energy homeostasis

Authors: *P. JOVANOVIC, H. CHODAVARAPU, L. CAMBIER, B. CHANG, C. E. RIERA
Diabetes and Obesity Res. Center, Dept. of Biomed. Sci., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Olfactory inputs are important for hedonic evaluation of food, resulting in food choice and possible consumption. Olfactory acuity is determined by the feeding status, with hunger enhancing smell and food seeking behavior, whereas satiety suppresses olfaction and promotes energy expenditure. Efforts to understand the cellular basis of food intake and energy expenditure revealed the crucial role of the hypothalamus as a master regulator of whole-body energy homeostasis, integrating internal and external stimuli to modulate energy intake and expenditure accordingly. However, how the hypothalamus adjusts circuits regulating energy homeostasis depending on external stimuli, such as smell, remains an intriguing mystery. Our previous work revealed that ablation of olfactory sensory neurons (OSNs) stimulates hypothalamic-driven autonomic tone and promotes catabolic pathways, enhancing thermogenesis in adipose tissue. These findings unravel a new function for the olfactory system in controlling energy homeostasis in response to sensory signals. Here, we analyzed neural circuits connecting olfaction and hypothalamus and determined the role of olfactory inputs on energy homeostasis. To identify neural circuits linking olfactory and hypothalamic neurons, we conducted anterograde viral tracing from mitral cell layer in the main olfactory bulb (MOB) in Tbx21-Cre mice and retrograde viral tracing from pro-opiomelanocortin (POMC)- and agouti-related protein (AgRP)-expressing hypothalamic neurons in POMC-Cre and AgRP-IRES-Cre mice using Cre-dependent helper virus and modified rabies virus. Additionally, we used chemical ablation of mature OSNs and chemogenetic silencing of mitral cell layer neurons to determine the effect of olfaction on energy homeostasis. Viral tracing revealed that piriform cortex (PC)-amygdala (Amy)-arcuate nucleus of hypothalamus (ARC) is one of the plausible circuits responsible for transferring signals from OSNs to the hypothalamus. Our data shows that upon chemical ablation of mature OSNs in the olfactory epithelium a decrease in a number of c-fos positive cells in PC and ARC occurs in animals that are refed after fasting compared with control ones. This data indicates that loss of smell, in addition to impacting olfactory pathways, also affects neuronal activity in the ARC, and therefore is likely to alter energy homeostasis. Further studies with probing circuits linking olfaction and hypothalamus will be required to determine their role in modulating energy homeostasis.

Disclosures: P. Jovanovic: None. H. Chodavarapu: None. L. Cambier: None. B. Chang: None. C.E. Riera: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.09/QQ19

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant 3R01MH074457-11S1

Title: Elevated blood creatinine correlating with gray matter atrophy? A novel finding with far-reaching implications

Authors: *E. KOTKOWSKI¹, P. T. FOX², L. R. PRICE⁴, C. G. FRANKLIN², M. SALAZAR³
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Abstract: The relationship between kidney function biomarkers, neurocognitive function, and brain anatomy are poorly understood. Parallels between the vascular effects off hypertension, hyperglycemia, insulin resistance, and obesity in the kidney and brain have been previously hypothesized, yet few studies have attempted to probe the relationship. One hypothesis suggests that the oxidative stress leading to endothelial cell damage in the renal vasculature due to metabolic diseases such as type II diabetes, hypertension, and metabolic syndrome is similar to that of the brain's and is most pronounced in the brain regions with higher oxygen demand such as the hippocampus and insula. A cross-sectional analysis was conducted using a voxel-based morphometry and general linear model mass univariate approach involving T1-weighted brain scans of 800 Mexican-Americans from the Genetics of Brain Structure dataset. Multivariate models adjusted for age and sex were used to test for associations between kidney function biomarkers, creatinine and blood urea nitrogen, and gray matter volume. Mean total subject age (n = 800, 44% male and 56% female) was 34.9 ± 14.3 (SD). In the fully adjusted mass univariate analysis, higher creatinine levels correlated significantly ($p < 0.001$) with lower gray matter volume in the orbitofrontal cortex, caudate nuclei, hippocampi, parahippocampal giri, and insular cortices; regions overlapping with the meta-analytically derived hippocampal network model. Further analyses using BrainMap suggest that these regions are significantly associated with reward paradigms ($z = 8.3$) and neuropsychiatric diseases such as Alzheimer's dementia ($z = 10.6$), mild cognitive impairment ($z = 5.1$), and frontotemporal dementia ($z = 4.8$). Although much work still needs to be done to characterize the mechanisms and pathways underlying our observations, these preliminary findings suggest a significant correlation between specific brain regions and kidney function in a normally distributed population and may serve as future potential biomarkers for neurocognitive function.

Disclosures: E. Kotkowski: None. P.T. Fox: None. L.R. Price: None. C.G. Franklin: None. M. Salazar: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.10/QQ20

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Washington Research Foundation Fellowship

Title: The role of AgRP neurons in shaping the composition and energy harvest capacity of the gut microbiota

Authors: *S. EWBANK^{1,2}, C. A. CAMPOS^{1,2}, S. L. PADILLA^{1,2}, A. J. BOWEN^{1,2}, J. L. DEMPSEY³, J. Y. CUI³, R. D. PALMITER^{1,2}

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Abstract: The gut microbiota plays an important role in host energy homeostasis. Since energy homeostasis is essential for survival, it is plausible that neural circuits involved in maintaining host energy homeostasis would evolve to shape the composition of the gut microbiota in alignment with the energy needs of the host. In humans and mice, neurons expressing agouti-related protein (AgRP neurons) in the arcuate nucleus of the hypothalamus play an important role in stimulating food intake and maintaining energy balance. AgRP neurons are maximally active during starvation conditions; thus, we are investigating whether they help conserve energy under these conditions by altering the composition of the gut microbiota to a state with a greater capacity for energy harvest. We investigated this hypothesis by chemogenetically activating AgRP neurons in male and female mice under three different feeding paradigms (fed *ad libitum*, pair-fed with control mice, and food-restricted to match the bodyweights of control mice) for a 10-day period and analyzing the subsequent bacterial composition and energy harvest capacity of the gut microbiota of these mice relative to unstimulated control mice. We assessed the bacterial composition of the gut microbiota using 16S rRNA amplification, sequencing, and characterization (n = 23), and we assessed the energy harvest capacity of the gut microbiota by determining the gross energy content of the mouse fecal matter using bomb calorimetry (n=24). Our preliminary findings suggest that AgRP neuronal activation can shape the gut microbiota composition to a state previously found to be associated with greater energy harvest capacity. This finding could contribute to a better understanding of why and how gut microbiota changes occur, which may be relevant to understanding metabolic diseases such as obesity.

Disclosures: S. Ewbank: None. C.A. Campos: None. S.L. Padilla: None. A.J. Bowen: None. J.L. Dempsey: None. J.Y. Cui: None. R.D. Palmiter: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.11/QQ21

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Involvement of specific phospholipase C beta subtypes in serotonin 2C receptor activation of arcuate POMC neurons

Authors: *J. CHOI, J.-W. SOHN
KAIST, Daejeon, Korea, Republic of

Abstract: Serotonin 2C receptors expressed by the pro-opimelanocortin (POMC) neurons within the arcuate nucleus of hypothalamus control food intake, energy expenditure, and glucose homeostasis. Previous studies have shown that serotonin 2C receptor agonists activate arcuate POMC neurons via TRPC5 channels. Serotonin 2C receptors belong to the Gq-protein coupled receptor (GqPCR) subfamily, and it was suggested that phospholipase C (PLC) is involved in the acute effects of serotonin 2C receptor agonists. However, it remains unclear which specific PLC beta subtypes are involved in this effect. In this study, we characterized expression of specific PLC beta subtypes by arcuate POMC neurons. We also tested involvement of identified PLC beta subtypes in the acute effects serotonin 2C receptor agonists on arcuate POMC neurons. Results obtained from these experiments should further our understanding of cellular mechanisms responsible for the excitation of anorexigenic POMC neurons by serotonergic agents including Belviiq, a recently developed diet pill targeting serotonin 2C receptors.

Disclosures: J. Choi: None. **J. Sohn:** None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.12/QQ22

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: DFG GU 227/21-1

Title: Glucose metabolism of the avian brain: an FDG-PET study in pigeons (*Columba livia*) with estimated arterial input function of anesthetized and awake state

Authors: *K. VON EUGEN¹, F. STRÖCKENS¹, H. BACKES², H. ENDEPOLS³, O. GUNTURKUN¹

¹Ruhr-University Bochum, Bochum, Germany; ²Max Planck Inst. for Metabolism Res., Cologne, Germany; ³Univ. Hosp. of Cologne, Cologne, Germany

Abstract: Recently it was found birds have higher neuron packing densities compared to mammals. In fact, songbirds and parrots hold twice the number of neurons compared to similarly sized primate brains. The downside of having many neurons are the energetic costs linked to the both the sustenance of these neurons and the demands of synaptic activity. Indeed, in humans the brain accounts for 20% of all consumed glucose at rest. Interestingly, there is a fixed energy budget per neuron across mammalian species, thus it is the absolute number of neurons that influences the increased energy costs of larger brains. As of now, it is unclear whether avian

brains have comparable energy demands, and how they are able to sustain such high numbers of neurons. This study sets out to unravel the neuroenergetics of the avian brain making use of 2-deoxy-2[¹⁸F]fluoro-d-glucose positron emission tomography (FDG-PET), which is a powerful tool widely used to assess cerebral glucose metabolism. In pigeons, this was combined with arterial blood sampling to measure an arterial input function. This type of kinetic modelling allows for a quantitative evaluation of FDG uptake. Moreover, we assessed the differences in FDG-uptake following an intravenous or intraperitoneal FDG bolus injection, and compared both in awake and anesthetized state. We were able to obtain an input function, and combine it with available neuron numbers to estimate the average glucose use per neuron in the pigeon brain. Moreover, we found expected differences between anesthetized and awake state, and quantified the effects of FDG administration route.

Disclosures: **K. Von Eugen:** None. **F. Ströckens:** None. **H. Backes:** None. **H. Endepols:** None. **O. Gunturkun:** None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.13/QQ23

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Research Foundation of Korea

Title: Excitation of neurons in DMV brain regions directly regulate hepatic lipid synthesis and gluconeogenesis gene expression

Authors: ***W. SONG**, C. NAMKOONG

Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Aim: Compared to neuronal effects on food intake and energy expenditure studies, role of the neuronal circuitry and its function between nervous system and metabolic organs in the perspective of pathogenesis of obesity and diabetes is poorly understood. To elucidate the direct role of neurons in DMV region through parasympathetic nervous system on hepatic both lipid and glucose homeostasis.

Methods: We used Designer Receptors Exclusively Activated by Designer Drugs-based chemogenetic tools to control neuronal activities. We injected the virus expressing the hM3Dq DREADD by stereotaxic surgery targeting Dorsal Motor nucleus of the Vagus (DMV) neurons in the mouse brain. After recovery, we activate hM3Dq-DREADD transduced neurons by clozapine-N-oxide (CNO), specific DREADD ligand. To exam the effect of neuronal activation on regulation of the liver metabolism, liver tissue is collected for gene expression study and immunohistochemistry analysis.

Results: We confirm that our chemogenetic virus and mouse model is working by electrophysiology of DMV neurons showing that CNO activates the neurons. We performed liver tissue clarity and immunohistochemistry analysis to confirm 3D-anatomical interaction of parasympathetic neurons and hepatocytes. The images show complex and dense neuronal circuit in the liver. To further dissect the metabolic pathways in the liver by which parasympathetic nervous system controls lipogenesis and gluconeogenesis, we analyzed gene expression of key hepatic enzymes and present the expression fold change compared to each control including acetyl-coenzyme A carboxylase alpha (ACC1), fatty acid synthase (FAS), peroxisome proliferator-activated receptor α (PPAR α), Peroxisome proliferator-activated receptor γ coactivator 1- α (PGC1 α), Glucose 6-phosphatase (G6P) and Phosphoenolpyruvate carboxykinase 1 (PCK1).

Lipogenesis	mean difference \pm SEM	P value
ACC1	2.344 \pm 0.3811	P<0.0001
FAS	2.816 \pm 0.5994	P=0.0003
PPAR α	0.06432 \pm 0.6366	P=0.9210
PGC1 α	4.017 \pm 1.32	P=0.0088
Gluconeogenesis		
G6P	1.573 \pm 0.7362	P=0.0507
PCK1	3.032 \pm 0.9399	P=0.0061

Conclusion/Discussion: In this study, anatomical approach reveals the parasympathetic nerve system and hepatic tissues innervation. Acute activation of neurons in DMV results in increasing hepatic lipogenesis and gluconeogenesis. In addition to free fatty acids and hormones, the parasympathetic nervous system might be involved in the regulation of lipid and glucose metabolism.

Disclosures: W. Song: None. C. namkoong: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.14/QQ24

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation
 NOVO-Nordisk Foundation
 Danish Medical Research Council
 NORDEA Foundation

Center for Healthy Aging
Fondation Leducq
Dept of Clinical Neurophysiology, Rigshospitalet Glostrup

Title: Optogenetic stimulation and NMDA + AMPA receptor blockade reveal lack of association between cortical gamma activity and brain O₂ use

Authors: M. K. DAHLQVIST, *K. J. THOMSEN, M. J. LAURITZEN
TransNeurogroup, Copenhagen University, Inst. of Neurosci., Kobenhavn N, Denmark

Abstract: Gamma activity arises as an interaction between pyramidal neurons and parvalbumin interneurons (PV-INs) where PV-IN activity creates time windows within which pyramidal cells can fire action potentials. Gamma activity is related to attention and perception and believed to be highly energy consuming. Cortical gamma activity is highly dependent upon substrate supply via cerebral blood flow (CBF), but the relation between gamma activity in vivo and O₂ use is incompletely understood. Activity of NMDAR on PV-IN contributes to the gamma rhythm as knock-out of NMDAR in PV-INs halves gamma activity. We here examined the relation between stimulation-induced cortical gamma activity, NMDAR function and the cerebral metabolic rate of oxygen (CMRO₂). 3-5-month-old transgenic mice with channelrhodopsin-2 (ChR2) expressed in neocortical pyramidal neurons were used. The mice were stimulated either by whisker pad stimulation (15 s, 2 Hz, 1.5 mV, 1 ms pulses) or optogenetically with blue laser light (473 nm, 15 s, 2 Hz, 100 ms pulses). Tissue partial pressure of oxygen, extracellular field potentials (LFP) and CBF responses were monitored. Blockers of glutamate receptors were applied in the following order: first MK-801 (300 μM) (N-methyl-D-aspartate receptor (NMDAR) blocker) was applied alone and then together with NBQX (200 μM) (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) blocker). Whisker pad stimulation induced LFP, CBF and CMRO₂ responses that were abolished by NMDAR and AMPAR blockade. In comparison, optogenetic stimulation induced CBF and CMRO₂ responses that were unaffected by blocking NMDAR. Subsequent additional AMPAR blockade potentiated CBF without affecting CMRO₂ responses. This suggests that during combined NMDAR and AMPAR blockade, optogenetic stimulation activated only glutamatergic neurons and that synaptic cross-talk between neurons did not contribute to the CMRO₂ responses. Gamma power and CMRO₂ responses evoked by optogenetic, respectively whisker pad stimulation, correlated linearly, while no correlation between gamma and CBF responses was found at all. Blocking NMDARs reduced gamma responses significantly by ~24% during optogenetic stimulation and ~50% during whisker pad stimulation and parallel-shifted the linear correlations between gamma and CMRO₂ without affecting the slopes. Subsequent blockade of AMPARs abolished gamma responses to both stimulation types. Thus, during AMPAR blockade with inhibited neuronal cross-talk, CMRO₂, but not gamma, responses were evoked optogenetically, suggesting that CMRO₂ may be driven by neuronal activity independently of attendant gamma.

Disclosures: M.K. Dahlqvist: None. K.J. Thomsen: None. M.J. Lauritzen: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.15/QQ25

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSERC

Title: The effect of GLUT1 and MCT1 inhibition on cerebral glucose and lactate levels following intraperitoneal injections of metabolic fuels in mice

Authors: *A. BELAND, D. YAZJI, C. MESSIER
Psychology, Univ. of Ottawa, Ottawa, ON, Canada

Abstract: While glucose is the main energy substrate for the brain, the role of lactate as a source of energy remains controversial. Studies have shown that lactate and glucose levels in the extracellular compartment (ECC) of the brain show opposite fluctuations to their levels in the blood following intraperitoneal (i.p.) injections of metabolic fuels; an increase in blood lactate levels was accompanied by an increase in brain ECC glucose levels, while brain ECC lactate levels remained relatively stable.

We tested a hypothesis suggesting that the increase in blood lactate is directly responsible for the increase in brain ECC glucose. We administered i.p. injections of glucose (GLUT1) and monocarboxylate (MCT1; lactate transporter) transport inhibitors, WZB117 and AZD3965 respectively, to adult male CD-1 mice (as well as the 50% DMSO vehicle). After GLUT and/or MCT1 inhibition, systemic metabolic homeostasis was altered by i.p. injection (2g/kg) one of the following metabolites: glucose, lactate or fructose.

We found that injections of either GLUT1 or MCT1 alone blocked the increase in brain glucose levels, even with blood lactate levels that were transiently higher than control.

Mice that received lactate injections subsequent to MCT1 inhibition had increased blood lactate levels and suppressed brain glucose levels compared to control.

However, glucose injections coupled with GLUT1 inhibition attenuated the rise in blood lactate while causing an increase in brain glucose.

Fructose injections caused general decreases in brain lactate levels while increasing blood glucose 30 minutes post metabolite injection.

Our results indicate that there is a complex interaction between the brain's energy demand, transport and the body's systemic metabolic availability. This research alludes to the brain's capacity to use complex and adaptable mechanisms to compensate for imposed energy restrictions and availability.

Disclosures: A. Beland: None. D. Yazji: None. C. Messier: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.16/QQ26

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: The Leverhulme Trust Grant RPG-2017-404

Title: Metabolic cost of plasticity shapes synaptic plasticity rules, a computational modeling study

Authors: *H. LI, M. C. VAN ROSSUM

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Abstract: The brain makes up only 2% of the body mass but consumes 20% of the body's metabolic energy at rest. While in today's society where the brain's metabolic need can be met by easily accessible high caloric food, from an evolutionary perspective, energy efficiency might have been an important driving force in shaping neural computation from the biophysical to the network level. So far, sparse coding, synaptic depression and details of voltage-gated ionic currents have all been attributed to energy efficient computation, but no theoretical work on the impact of energy efficiency on synaptic plasticity and learning has been conducted yet. Experimental research has suggested that changing the synaptic strength between neurons requires particularly large amounts of energy. For instance, in an experiment performed by Mery and Kawecki, when fruit flies were subjected to associative conditioning, the fly's survival time was reduced by 20% after their food supply was cut off, compared to flies that were not exposed to the association. We wondered how synaptic plasticity should be organized so that it can achieve powerful learning that is also time energy efficient. Hereto we implemented a simple neuron model that has been used to model the cerebellar purkinje cells, a perceptron, and quantified the metabolic energy as the sum of the absolute changes in the synapses. We measured how much metabolic energy was needed for the perceptron to successfully learn a binary classification problem with different learning algorithms and learning rates. We found that the classical perceptron learning rule is energy inefficient. However, batch learning - a well known method from machine learning, where many patterns are presented and tested before the synapse is updated - is much more energy efficient than when the synapses are being updated after each input presentation. Lastly we determined an energy-saving scheme to optimize task performance with respect to energy efficiency.

Disclosures: H. Li: None. M.C. Van Rossum: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.17/RR1

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01NS07224107
NIH 1F31NS102151-01A1

Title: Brain-specific loss of long-chain fatty acid oxidation

Authors: *C. J. WHITE¹, J. LEE², J. CHOI¹, E. SELEN ALPERGIN¹, M. J. WOLFGANG¹
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Abstract: The central nervous system (CNS) requires the consumption of 20% of all energy substrates in humans for proper function. Generally, many consider glucose as the exclusive metabolic substrate in the brain save ketone bodies in disparate conditions. Recently, it has been shown that the CNS is capable of oxidizing glutamate, glutamine, and lactate. The CNS is the most lipid-rich tissue in humans other than adipose. Fatty acids (FAs) are more energy dense than glucose and little is known about their oxidation in the CNS. Despite little study, CNS FA metabolism (FAM) is necessary for proper neuronal function. Inborn errors in FAM in humans including X-ALD and Sjögren-Larssen Syndrome lead to neurological impairments. None of the aforementioned disorders are the result of impairments to long-chain (LC) FAO. The capacity for CNS FAO has been contested due to mixed brain culture murine mitochondria only having 0.7% the specific activity of the FAO enzyme 3-ketoacyl CoA thiolase compared to heart mitochondria. Despite this, FAO of ¹⁴C palmitate has been shown in murine primary astrocytes. The purpose for CNS FAO could include but may not be limited for energy in basal or disparate conditions, lipid turnover, or for other uncharacterized roles. The hypothesis for this proposal is that the pan-brain loss of LC FAO may impact flux of substrates and behavior.

We will study the capacity for CNS FAO using mice with a floxed carnitine palmitoyltransferase 2 (*Cpt2*) gene. *Cpt2* protein is required for mitochondrial entry of LCFAs for FAO. *Cpt2* floxed mice (fl/fl) crossed with transgenic Nestin-Cre mice resulted in a pan-brain loss of FAO (*Cpt2*^{B-/-}). Metabolic phenotyping of fl/fl and *Cpt2*^{B-/-} mice including measuring weights over 15 weeks, blood glucose and serum metabolites resulted in no significant differences between genotypes. FAO of ¹⁴C oleate was measured in hippocampal (hipp) explants and in P2 primary cortical astrocytes. In hipp explants, FAO was depleted but not significantly in *Cpt2*^{B-/-} mice. In astrocytes, there is a greater than 3-fold reduction in oleate oxidation. A relative metabolite summary was generated using LC-MS/MS with 24-hr fasted hipp from fl/fl and *Cpt2*^{B-/-} mice. 20-fold increases in LC acylcarnitines (ACs) were observed in *Cpt2*^{B-/-} hipp indicating incomplete FAO. Overall, these data suggest a capacity for FAO in brain.

Future experiments include the validation of elevated ACs in Cpt2^{B-/-} mice through quantitative MS/MS. Cell-type specific metabolic profiles in primary Cpt2^{B-/-} astrocytes will be determined using ¹H NMR. To determine the purpose of FAO in astrocytes, ¹⁴C oleate oxidation will be measured after stress via LPS, cold shock, or glucose deprivation.

Disclosures: C.J. White: None. J. Lee: None. J. Choi: None. E. Selen Alpergin: None. M.J. Wolfgang: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.18/RR2

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Marquette University Start-up Fund

Title: The effect of bromocriptine, a D2 receptor agonist, in lean and obese mice

Authors: *S. N. FRAMNES, E. BAKKE, D. M. ARBLE
Biol. Sci., Marquette Univ., Milwaukee, WI

Abstract: Type 2 Diabetes is a metabolic disorder that affects an estimated 415 million people worldwide. Bromocriptine, a D2-dopamine receptor agonist, has been shown to increase insulin sensitivity and reduce hyperglycemia through an unknown mechanism. Despite bromocriptine's known effect on glucose metabolism, bromocriptine's effect in lean mice has not been well characterized. Here, we test the effect of 2-week treatment of bromocriptine (i.p. 8 mg/kg) in lean and diet-induced obese C57Bl/6J mice (male and females) to determine how diet and sex influences bromocriptine's effect on glucose tolerance. We find that bromocriptine reduces fasting glucose ~20 ng/ml independent of sex and diet condition. Moreover, bromocriptine significantly improves glucose tolerance in diet-induced obese male mice as evidenced by a reduction in the glucose tolerance area under the curve (AUC; 32136 ±1471 vs. 24255 ±859 after treatment). However, despite a reduction in fasting glucose, bromocriptine did not significantly improve the glucose tolerance of diet-induced obese female mice (25660±4025 vs 18164±4857 after treatment) These data indicate that while bromocriptine is effective at reducing fasting glucose, bromocriptine's ability to improve glucose tolerance is more variable in females. Further research into the sex-differences in bromocriptine's effectiveness can yield important clues for bromocriptine's mechanism of action.

Disclosures: S.N. Framnes: A. Employment/Salary (full or part-time);; Marquette University. E. Bakke: None. D.M. Arble: A. Employment/Salary (full or part-time);; Marquette University.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.19/RR3

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: impact of high fructose diet on neuronal development, metabolism and psycho-emotional behavior

Authors: *A. MENIGOZ¹, C. E. BARRETT², D. G. RAINNIE³

¹Psychiatry, Yerkes Natl. Primate Res. Ctr. - Emory Un, Atlanta, GA; ²Dept. of Psych. and Beh. Disorders, Emory Univ., Atlanta, GA; ³Emory Univ., Atlanta, GA

Abstract: Type 2 diabetes mellitus (T2DM) is now at epidemic proportions in the US population, with ~10% of the population having T2DM and 35% with pre-diabetic metabolic disorder. The incidence of T2DM in children has risen by > 30%. Children with T2DM are at increased risk of psychiatric disorders, suggesting commonalities in environmental etiology and neural circuitry early in development. Aberrant activity of basolateral amygdala (BLA) principal neurons is thought to be critically involved in the pathophysiology of psychiatric disorders, many of which emerge early in life. We hypothesized that pre-weaning exposure to a high fructose diet (pw-HFrD) would disrupt normative development of BLA principal neurons and be associated with behavioral abnormalities. We examined socioemotional and cognitive behavior, the metabolism and single cell BLA gene expression across development in pw-HFrD and control rats. Pw-HFrD lead to a behavioral profile of hyperactivity and increased risk taking as evidenced by increased distance traveled in the open field in males, reduced time spent immobile in a forced swim test in both males and females and increased time in the open zones of an elevated-O maze in males and females. Pw-HFrD males also displayed impaired attention and a decreased inhibition behavior as measured in the operant conditioning Go/Nogo task. pw-HFrD causes premature expression of insulin and insulin-like growth factor receptor mRNA prior to weaning and abnormally elevated levels of *Igfr* mRNA even after weaning. pw-HFrD also causes significant changes to the expression of *Ampk* subunits and other components of the AMPK signaling cascade. We would predict that disruptions of this pathway during key periods of development resulting from a pw-HFrD could likely result in long-lasting and deleterious effects on the extended amygdala and other brain regions, leading to the development of an ADHD like phenotype. Uncovering disruptions in metabolic pathways shared between juvenile-onset diabetes and attention disorders may be a crucial step in developing new therapeutic strategies effective at improving the physical and psychological health of those suffering from these metabolic disorders.

Disclosures: A. Menigoz: None. C.E. Barrett: None. D.G. Rainnie: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.20/RR4

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant DK090823

Sigma Xi G2017031588446675

American Heart Association 16GRNT31110008

Title: Innervation has distinct impact on global transcriptome of white and brown adipose tissues

Authors: Q. ZHU¹, J. CAO¹, L. LIU¹, C. LIANG¹, *H. SHI²

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Abstract: Due to the globally increasing incidence of obesity, much attention is paid to studying the physiological regulation of white and brown adipose tissues (WAT and BAT, respectively). Increased lipid storage and related chronic inflammation at abdominal retroperitoneal WAT (RWAT) and epididymal (EWAT), but not subcutaneous inguinal WAT (IWAT), is associated with adverse effects of obesity. WAT and BAT are innervated by the sympathetic nervous system that regulates lipid metabolism and cytokine production in WAT and lipid oxidation and thermogenesis in BAT. Dampened sympathetic activity has been reported in obesity, leading to dysfunction of lipid metabolism and chronic inflammation. Unilateral, surgical denervation of WAT and BAT increase lipid accumulation comparing to their contralateral, intact within animal control fat depot, implying dysregulation of lipid metabolism following denervation. Detailed analysis on gene expression of various WAT and BAT by innervation has not been provided yet. We hypothesized that genes involved in lipid metabolism, inflammation, cytokine production and thermogenesis are regulated by innervation and are dependent on lean or obese state of animals. Adult male C57BL/6J mice were fed a low-fat diet or a high-fat diet for four weeks, and received unilateral denervation at interscapular BAT, EWAT, RWAT, and IWAT. After mice recovered from the surgeries, the aforementioned WAT and BAT were collected and RNA was isolated for sequencing. Differential gene expression analysis was performed by DESeq2, with adjusted P value less than 0.01 and a log₂ fold change greater than 1.5 being considered differentially expressed between intact and denervated tissues. Biological characteristics associated with these genes were investigated using ClueGO. Denervation did not significantly affect gene expression in BAT of lean or obese mice, possibly due to compensatory regulation by circulating factors. In contrast, denervation of EWAT, IWAT, and RWAT of lean and obese mice similarly upregulated genes related to immune response, inflammation, chemokine signaling pathway, and mitotic cell cycle; while downregulated genes involved in fatty acid and lipid metabolic process, insulin signaling pathway, and fat cell differentiation. Upregulated genes

involved in immune response in denervated WAT could be due to tissue injury and trauma related to the surgeries. Although it was surprising that denervation had similar effects on lipid metabolism between subcutaneous and abdominal WAT, downregulation of genes involved in lipid metabolism by denervation confirmed important role of sympathetic innervation in energy metabolism.

Disclosures: Q. Zhu: None. J. Cao: None. L. Liu: None. C. Liang: None. H. Shi: None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.21/RR5

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01EY027077 NIH-NEI
R01EY027711 NIH-NEI

Title: Deep brain photoreception: An opsin-5 dependent hypothalamic-adipose neuraxis

Authors: *K. ZHANG, B. A. UPTON^{1,6,2,3}, S. VEMARAJU^{4,2}, G. NAYAK^{4,2}, J. A. MOCKO⁴, R. A. LANG^{4,2,5,7}

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Abstract: The thermogenic potential of brown adipose tissue (BAT) is a promising therapeutic target in the treatment of obesity and metabolic disorders. The preoptic area (POA) is a region in the anterior hypothalamus responsible for autonomic thermoregulation by means of modulating BAT activity through sympathetic nerve activity (SNA). Neurons in the POA express opsin-5 (OPN5), an atypical opsin found in various extraretinal tissues and known to respond to near-UV wavelengths with a lambda-max of 380 nm. OPN5 has previously been shown to regulate seasonal breeding behavior in birds. We have also shown OPN5 to be required in retinal ganglion cells for *in vivo* entrainment of a retina circadian clock independent of the suprachiasmatic nucleus. To date, no other physiological role has been proposed for OPN5. The same POA neurons that express OPN5 also engage the central thermoregulatory circuit that modulates BAT activity. Our data, in combination with published findings, supports the hypothesis that the mammalian autonomic thermoregulatory apparatus is light responsive. Using a genetically targeted glycoprotein-deleted rabies virus injected into the POA, we identified labeled neurons in the rostral raphe pallidus (rRPa), the lateral parabrachial nucleus (LPB), and the dorsomedial hypothalamus (DMH), all nuclei known to participate in central

thermoregulation. To assess BAT activity, we acutely challenged OPN5 null mice and controls with a 4°C cold stress for 3-5 hours, and assessed core temperature. *Opn5*^{-/-} animals better defended their body temperature when subjected to cold, and were 1.1 ± 0.3 °C warmer than controls at the end of acute stress. BAT target gene transcripts (*Ucp-1*, *Prdm16*, *Pgc-1a*) were elevated in these cold stressed *Opn5*^{-/-} animals, highlighting the contribution of BAT-mediated thermogenic uncoupling, and not skeletal muscle shivering or cutaneous vasoconstriction, to this improved cold defense. Furthermore, C57BL/6J mice reared without 380 nm light phenocopy *Opn5*^{-/-} animals when acutely cold challenged, suggesting a mechanism where UV-sensitive hypothalamic OPN5 neurons regulate efferent thermosensory pathways in a sympathoexcitatory manner.

Disclosures: **B.A. Upton:** None. **S. Vemaraju:** None. **G. Nayak:** None. **J.A. Mocko:** None. **R.A. Lang:** None.

Poster

068. Brain Blood Flow, Metabolism, and Homeostasis: Energy Metabolism

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 068.22/RR6

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01EY027077 NIH-NEI
R01EY027711 NIH-NEI

Title: Opn3 (Encephalopsin) as a putative mammalian deep brain photoreceptor

Authors: ***B. A. UPTON**¹, K. ZHANG¹, S. VEMARAJU¹, A. SWEENEY², A. HOLT², E. BUHR³, R. VAN GELDER³, R. LANG¹

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Abstract: Atypical (i.e. nonvisual) opsins have been found within the central nervous system in nearly every class of the vertebrate subphyla. While functions of many of these opsins have been identified, research on mammalian atypical opsins have largely been limited to Opn4 (melanopsin). Opn3 (encephalopsin) is expressed throughout the mammalian brain, including within the cortex, striatum, thalamus, hypothalamus, subfornical organ, olfactory bulb, and cerebellum beginning during embryonic development and continuing into adulthood. Tissue from these regions can photoentrain *ex vivo*, independent of retinal or SCN connectivity. Using an optical microprobe, external light was measured *in vivo* from the surface of the brain and into the hypothalamus, resulting in a 2-3-log fraction decrease in 480 nm light intensity, the absorption maxima of Opn3. Additionally, a 2-log fraction decrease in 480 nm light was measured from the surface of a pregnant mouse into the uterus. Together, these results suggest

that Opn3 is capable of detecting ambient light within various cortical and subcortical nuclei of mice and may have a role in phototransduction during development and throughout adult life.

Disclosures: **B.A. Upton:** None. **K. Zhang:** None. **S. Vemaraju:** None. **A. Sweeney:** None. **A. Holt:** None. **E. Buhr:** None. **R. Van Gelder:** None. **R. Lang:** None.

Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.01/RR7

Topic: F.07. Autonomic Regulation

Support: NIH Grant HL-72125

Shanghai Natural Science Foundation Grant 16ZR1428300

Title: Role of hypothalamic opioids in moxibustion modulation of sympathoexcitatory cardiovascular reflex responses

Authors: ***Y. GONG**¹, **S. TJEN-A-LOOI**², **L.-W. FU**², **L. CHENG**³

¹Pharmaceut. Sci., ²Med., Univ. of California, Irvine, Irvine, CA; ³Shanghai Univ. of Traditional Chinese Med., Shanghai, China

Abstract: The paraventricular nucleus (PVN) regulates sympathetic outflow and blood pressure. Electroacupuncture stimulation of somatic sensory nerves decreases cardiovascular reflex responses through the hypothalamic PVN. Mechanical stimulation of acupoints decreases pressor responses through polymodal peripheral transient receptor potential vanilloid type-1 (TRPV1). Moxibustion generating heat is applied at acupoint to treat diseases such as hypertension but its mechanisms are unclear. We hypothesized that the PVN and peripheral heat sensitive TRPV1 participate in the modulation of sympathoexcitatory cardiovascular responses by moxibustion. Rats were anesthetized, ventilated, and heart rate and mean blood pressure were monitored. Gastric distention induced consistent pressor reflex responses every 10-min. Thirty-min of bilateral moxibustion at acupoint ST36, overlying the deep peroneal nerves, reduced the gastric distention evoked elevation in blood pressure. Moxibustion at an average of 44.2 °C in contrast to 40°C reduced the pressor responses. The moxibustion inhibition of the cardiovascular responses was reversed with iodoresiniferatoxin blockade of local ST36 peripheral TRPV1. Centrally, microinjection of naloxone, an opioid receptor antagonist, into PVN reversed the effect of moxibustion. Thus, the activation of hypothalamic PVN opioid system and peripheral TRPV1 contributed to moxibustion inhibition of sympathoexcitatory cardiovascular reflex responses.

Disclosures: **Y. Gong:** None. **S. Tjen-A-Looi:** None. **L. Fu:** None. **L. Cheng:** None.

Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.02/RR8

Topic: F.07. Autonomic Regulation

Title: Effects of breath-holding in central nervous system activities and autonomic nervous system activities

Authors: *T. KIKUCHI¹, M. TAKAYOSE¹, K. ARAI¹, K. FUJIMOTO², Y. SANO², K. SHIROISHI³, N. GYODA⁴

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Abstract: *[Background]* Drowsiness is often induced by monotonous work. About 10% of ship accidents occur as a result of operator dozing, causing serious accidents, including death. Therefore, the development of drowsiness mitigation methods that can be easily carried out during work is significant. The authors (2016, 2017) reported that breath holding alleviates subjective drowsiness. In this study, we examined the effects of breath-holding on central nervous system (CNS) activities and autonomic nerve system (ANS) activities as a physiological response supporting subjective drowsiness reduction. *[Method]* 9 healthy people volunteered as subjects. EEG power spectra were used as an indicator of CNS activities. Electrodes for recording EEG were placed on the scalp at Fz, Cz, C3, C4, Pz, O1 and O2. EEG power in the each frequency bands were expressed as a percentage of the total power (3-30 Hz). Pulse wave transmission time (PTT) was used as indicator of ANS activities. Pulse waves (obtained from forehead) and ECG (standard technique) were measured at the same time. Pulse waves was second derivative. It was calculated PTT from a peak point of second derivative pulse waves and ECG R-wave. As a monotonous task to induce drowsiness, the subjects performed a simple reaction task (SRT) by visual stimulation at the sitting position. Subjects performed breath-holding when drowsiness was caused. The breath-holding time was set to about 90% of the subjective maximum effort. The degree of subjective drowsiness was measured using a Visual Analog Scale (VAS). EEG and PTT were examined for 30 seconds change before and after breath-holding. *[Result]* VAS values were significantly reduced after breath-holding. SRT after breath-holding was shorter than before breath-holding, no significant difference was observed. The percentage of alpha band activity in all electrodes without Cz significantly decreased after breath-holding. The percentage of beta band activity in C3, C4, O1 and O2 significantly increased after breath-holding. PTT value showed a significantly increased after breath-holding. *[Conclusion]* As the percentage of alpha band activity decreased and the percentage of beta band increased after breath-holding, CNS activities increased and arousal level increased due to

breath-holding. In addition, since the PTT value increased after breath-holding, sympathetic nerve activity increased due to breath-holding.

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Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.03/RR9

Topic: F.07. Autonomic Regulation

Support: Horst Görtz Foundation

Title: Functional MRI of the brainstem and hypothalamus during lower body negative pressure: Sympathetic and parasympathetic rhythms in humans

Authors: *F. BEISSNER¹, J. MANUEL SANCHÉZ¹, N. NAZARENKO¹, K. HEUSSER², J. TANK², J. JORDAN²

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Abstract: Introduction: The sympathetic and parasympathetic nervous system both exhibit characteristic oscillatory behaviours. Oscillations of the sympathetic efferents at ~0.1 Hz tightly couple with arterial blood pressure oscillations (Mayer waves). It is still unclear, whether Mayer waves are the result of a central pacemaker or a resonance phenomenon of the baroreflex and other feedback loops. Oscillations of the parasympathetic system are triggered by respiration, leading to the so-called respiratory sinus arrhythmia that modulates heart rate at a frequency of ~0.25 Hz. Here, we combined fMRI with lower body negative pressure (LBNP) and concomitant autonomic recordings to induce the baroreflex, thus changing the sympathetic and parasympathetic outflow. Our hypothesis was that such an approach would increase both sympathetic and parasympathetic oscillations and that their characteristic frequencies could be used to detect hypothalamic and brainstem centres involved in this oscillatory activity.

Methods: 22 healthy subjects were scanned on a 3T MR scanner. The protocol involved SMS-EPI functional scans (voxel size=2x2x2 mm³) and a T1-weighted structural scan (voxel size=1x1x1.2 mm³). LBNP stimulation of -30mmHg was delivered for two blocks of five minutes length using a custom-made MR-compatible pressure chamber and a vacuum cleaner controlled by a digital pressure gauge. FMRI data were minimally preprocessed using motion correction, unwarping, temporal high-pass filtering and normalisation to a study template. A simple power density spectral analysis of the functional data was conducted, to extract the RSA (0.25 ± 0.5 Hz) and Mayer (0.1 ± 0.035 Hz) bands. The effect of LBNP was quantified using a

paired t-test.

Results: We found spectral changes related to the LBNP paradigm in multiple nuclei in the hypothalamus and brainstem. In the Mayer band, we observed changes in the Lateral Hypothalamus, the Paraventricular Nucleus and in the Arcuate Nucleus. In the mesencephalon the Substantia Nigra and the Parabrachial Nucleus exhibited changes; as well as the Rostral Ventrolateral Medulla in the lower brainstem. The LBNP paradigm also triggered changes in the RSA band, mostly in the hypothalamus. In this band, we observe changes in the Lateral Hypothalamus, the Paraventricular Nucleus and in the Arcuate Nucleus.

Conclusion: Spectral analysis of the BOLD signal is a simple but powerful tool for studying oscillations in the central nervous system. Our results show that selected nuclei in the hypothalamus and brainstem are linked to Mayer waves. Furthermore, we observe regions in the hypothalamus oscillating at the RSA frequency.

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Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.04/RR10

Topic: F.07. Autonomic Regulation

Title: Comparing implantable and non-invasive bioelectronic medicines using cardiopulmonary physiology and machine learning, towards closed-loop therapy systems

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Abstract: Bioelectronic medicine is an emerging discipline of therapeutics seeking to treat disease using neural stimulation. In this context, neural stimulation is usually achieved using an implanted interface, requiring surgery and significant costs. Using a non-invasive neural stimulation interface for therapy would potentially enhance access to a broader patient population, while reducing the cost of treatment. Here we assess the hypothesis that non-invasive stimulation of neural circuits of the outer ear produces robust and selective cardiopulmonary

effects, compared to implanted cervical vagal nerve stimulation. We performed our experiments in anesthetized rats. Non-invasive stimulation was performed at sites on the outer ear through a novel mixed ionic electronic conducting dry electrode interface. Invasive stimulation of the left cervical vagus nerve was performed using an implanted bipolar cuff electrode. We recorded the electrocardiogram, arterial blood pressure (ABP), and the photoplethysmogram during systematic assessment of stimulation protocols. Our preliminary results support the hypothesis that selective control of ABP can be achieved via non-invasive stimulation, without significant side effects (e.g. bradycardia or bradypnea). These results have implications for wearable bioelectronic medicine devices to treat hypertensive states. We will present our current results using machine learning to decode both neural stimulation events and disease state indicators (e.g. a spontaneous hypertensive crisis). These experiments address the hypothesis that machine learning can be used to decode critical biomarkers needed for closed-loop bioelectronic medicines. Our future work will focus on decoding pathological activity from wearable sensors for triggering non-invasive stimulation of neuromodulatory circuits. Our goal is to develop wearable closed-loop bioelectronic medicines for treating an array of debilitating diseases.

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Poster

069. Recent Advances in Cardiovascular Regulation

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.05/RR11

Topic: F.07. Autonomic Regulation

Support: UCLA Clinical and Translational Science Institute Research Scholar Award to RK (UL1TR001881)

Title: Regional brain changes in patients with pulmonary hypertension

Authors: A. SAHIB¹, L. EHLERT¹, B. ROY², X. SONG¹, M. TOWNSLEY¹, S. SINGH¹, K. MCCLOY³, M. EGHBALI¹, R. SAGGAR³, *R. KUMAR^{1,4,5,6}

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Abstract: Pulmonary arterial hypertension (PAH) patients show a variety of symptoms, including autonomic, cognitive, depression and anxiety, and disordered breathing, in addition to issues related to primary condition. The abnormal functions suggest the presence of brain injury

in those regulatory areas that can be examined with non-invasive magnetic resonance imaging (MRI) procedures. However, the tissue integrity across the whole-brain in PAH patients is unclear. Our aim was to assess regional brain changes in PAH over control subjects using MRI-based diffusion tensor imaging (DTI) procedures. We acquired two DTI series from 7 PAH (age, 50.75 ± 6.0 years; body mass index, 30.2 ± 10.4 kg/m²; 3 male) and 20 healthy control subjects (age, 51.59 ± 6.7 years; body mass index, 27.1 ± 3.3 kg/m²; 10 male) using a 3.0-Tesla MRI scanner, and examined cognitive (Montreal cognitive assessment, MoCA), depression (Beck Depression Inventory II, BDI-II), anxiety (Beck Anxiety Inventory, BAI), and sleep status (Epworth Sleepiness Scale, ESS; Pittsburgh Sleep Quality Index, PSQI). Using diffusion and non-diffusion images, mean diffusivity (MD) values, which indicate average motion of water molecules within the tissue and show microstructural changes, with decreased values in acute, and increased in chronic pathological condition, were calculated at each voxel from each DTI series. Both MD maps, derived from each DTI series, were realigned and averaged, normalized to a common space, smoothed, and compared voxel-by-voxel between groups using ANCOVA (covariates, age and gender; SPM12, $p < 0.005$; extended threshold, 10 voxels). No significant differences in age, gender, body mass index, global MoCA, or ESS appeared between groups. However, significant differences were observed in PSQI ($p = 0.009$), BDI-II ($p = 0.002$), and BAI ($p = 0.001$) between groups. Various brain areas showed significantly increased MD values in PAH subjects, indicating predominantly chronic tissue changes, over controls. Sites with increased MD values were included the basal forebrain, left putamen, parietal, temporal, occipital and prefrontal cortices, bilateral insular cortices, anterior, mid, and posterior cingulate cortices, cerebellar vermis and crus, amygdala, hippocampus, and cerebellar cortices. PAH subjects show predominantly chronic tissue changes in areas that control mood, cognition, respiratory, and autonomic functions. The findings suggest that brain functional deficits in PAH have structural basis in the condition.

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Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.06/RR12

Topic: F.07. Autonomic Regulation

Title: Change in autonomic nervous responses in patients underwent dental occlusion treatment

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Abstract: We investigated the effect of dental occlusion treatment on autonomic nervous activity. Eleven adult dental patients (1 men, 10 women; mean and standard deviation 47.3 ± 13.9 years old), whose chief complaint is temporomandibular disorder, were participated in the study. All patients gave their written informed consent to participate. Individual dental occlusion was carefully evaluated prior to the experiment. We observed the difference in autonomic nervous activities between natural dentition without overlays (ND: natural dentition) and after wearing metal overlays which have appropriate shape that can guide the mandible to proper position (DTMO: dentition with true metal overlay). We measured the pupil light reflex using Iriscorder Dual C10641 (Hamamatsu Photonics, Shizuoka, Japan). Simultaneous electromyogram (EMG) of the masseter muscle and Electrocardiogram (ECG) were obtained using a multi-channel telemeter WEB-1000 (Nihon Kohden Co., Ltd., Tokyo, Japan). Participants performed mandibular grinding for 30 seconds, which was immediately followed by a recording of pupil light reflex and other inspections. In addition, participants performed another run of pupil light reflex after grinding with false overlays in order to determine the placebo effects of wearing metal overlays (DFMO: dentition with false metal overlay). Analyses were carried out observing the initial pupil diameter (D1) and minimum pupil diameter (D2) during the pupillary light reflex. Frequency components of heart rate variability (HRV) were analyzed into HF (High Frequency: 0.15~0.4 Hz) for parasympathetic nerve activities and LF/HF (Low Frequency: 0.04~0.15 Hz) for sympathetic nerve activities by wavelet transformation. We found a decreasing tendency in LF/HF component of HRV after grinding with DTMO, suggesting the suppressed sympathetic nervous activity. D2 in left eyes also showed a tendency of decrease after grinding with DTMO, suggesting the enhanced parasympathetic nervous activity. Grinding with DTMO further reduced the masseter muscle activity required for grinding. Our results suggest that appropriate mandible position can release the unnecessary muscle tension for grinding behavior and affect grinding-related changes in the autonomic nervous activity. Autonomic nervous activity has a potential to be an objective measure of therapeutic outcome in the treatment of dental occlusion.

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Poster

069. Recent Advances in Cardiovascular Regulation

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Program #/Poster #: 069.07/RR13

Topic: F.07. Autonomic Regulation

Support: The Fidelity Charitable Nancy Adams and Scott Schoen Fund and the Kraig and Linda Kupiec Family Trust

Title: Neuromodulatory effects of cranial and cervical nerve stimulation on migraine vs. trigeminal neuropathy pain

Authors: L. C. FEULNER¹, R. K. HARPER¹, G. TOBIN¹, E. P. NGUYEN¹, D. SNODGRASS², F. L. YAN-GO³, R. L. MERRILL⁴, E. K. SAUERLAND⁵, J. JEN⁶, *R. M. HARPER¹

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Abstract: Stimulating cranial nerves V, VII, IX, and X and cervical nerves C2 and C3 through mechanical vibration reduces migraine and trigeminal neuropathy pain and stabilizes blood pressure and heart rate. The relative effectiveness of the neuromodulatory procedure on migraine vs trigeminal neuropathy pain (burning mouth syndrome, oral pain from trauma, radiation-induced nerve injury, or temporal mandibular joint issues), or on cardiovascular and breathing patterns, however, is unclear. We evaluated changes in levels of pain perception, cardiovascular and respiratory patterns before and after 5 min sham vibration, followed by 15 min low amplitude vibration, 10 min high amplitude vibration, and a second 10 min sham vibration to cranial and cervical nerves in 36 migraine subjects (N=36, female =24, male =11) and 15 (female=10, male=5) trigeminal neuropathy pain subjects, aged 18-83 yrs. Subjects were referred by UCLA or Mayo Clinic neurologists or pain specialists. All procedures were approved by the UCLA Institutional Review Board. Pain levels were self-determined on a 0-10 pain scale. Vibratory stimulation at 128 Hz was delivered to the entire length of the external auditory meatus via custom silicon impressions. ECG, thoracic and abdominal wall movement, pulse oximetry, and pulse transit time (to infer beat-by-beat blood pressure) were acquired concurrently during the entire trial. Mean differences between pain levels pre- and post-intervention were calculated for both migraine and trigeminal neuropathy trials. Mean perceived pain levels decreased similarly for both migraine and trigeminal neuropathy subjects (migraine pre-post pain level differences: 3.95 ± 2.37 sd; trigeminal neuropathy: $3.25, \pm 2.54$). Heart and respiratory rates declined equivalently in both groups (migraine pre-HR=81, stimulation HR=77); (trigeminal neuropathy: pre-HR=73.5, stimulation=69.8); (migraine respiratory rate pre=20.4; stimulation=17.8); trigeminal neuropathy respiratory rate pre=19.2; stimulation=16.7). Blood pressure normalized; hypertensive systolic values declined, while hypotensive systolic values increased for both migraine and trigeminal neuralgia subjects. The findings suggest that the interventions are comparably useful for reducing both migraine and trigeminal neuropathy pain and they appear to affect physiological measures in a similar fashion in the two groups.

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Poster

069. Recent Advances in Cardiovascular Regulation

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Program #/Poster #: 069.08/RR14

Topic: F.07. Autonomic Regulation

Support: Canadian Space Agency
CIHR
NSERC

Title: Causality analysis of arterial baroreflex control following spaceflight and head-down tilt bedrest reveals a new mechanism for cardiovascular deconditioning

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Abstract: Background: Post-flight orthostatic intolerance remains a major concern for human missions involving long-duration weightlessness. There is increasing evidence that most changes affecting the cardiovascular system after return from space are induced by alterations of the autonomic neural control. Reduction of arterial baroreflex response has been observed after both short-term and long-term spaceflights. We hypothesize that prolonged unloading of the cardiovascular system weakens the coupling between blood pressure and heart rate. **Methods:** We conducted retrospective analysis of cardiovascular data collected from astronauts ($n=26$, 39 ± 5 years) who took part in shuttle missions lasting 8 to 16 days. These were compared with male volunteers ($n=19$, 35 ± 7 years) who completed 60 days of HDTBR at the MEDES research facility (Toulouse, FR). In each group, a supine-to-stand test with at least 5-min stand was conducted around 10 days before launch or HDTBR, and within 90 minutes of landing or exiting bedrest. Beat-by-beat systolic blood pressure (SBP) and R-to-R intervals (RRI) were collected simultaneously. Wavelet transform coherence analysis and convergent cross mapping causality methods were used to extract indices characterizing the interaction time (*percent time active*), response gain value (*gain*), and control directionality (*causality*) between SBP and RRI (SBP to RRI) during standing. All data are presented as mean \pm SD. **Results:** Following spaceflight, the arterial baroreflex percent time active was reduced ($30\pm 14\%$ to $22\pm 14\%$, $p<0.05$) along with causality (0.95 ± 0.03 to 0.93 ± 0.06 , $p<0.05$). Much larger reductions were seen with HDTBR. Percent time active decreased from $48\pm 13\%$ to $29\pm 15\%$ ($p<0.001$) and causality decreased from 0.94 ± 0.02 to 0.81 ± 0.17 ($p<0.001$). No change was observed in standing arterial baroreflex gain following spaceflight (7.6 ± 4.1 to 7.8 ± 7.0 ms/mmHg) but a large reduction was seen post-bedrest (7.7 ± 4.4 to 1.8 ± 1.5 ms/mmHg, $p<0.001$). **Conclusion:** These results indicate that the link between SBP and RRI was adversely affected by CV-unloading, and that the effect increased with time of exposure. With spaceflights now planned for up to one year, these new observations

point to a possible worsening of baroreflex control and the need to address this new mechanism for deconditioning.

Disclosures: **A.P. Blaber:** None. **D. Xu:** None.

Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.09/SS1

Topic: F.07. Autonomic Regulation

Support: CESNA

Title: Intracranial pressure is a determinant of sympathetic activity

Authors: ***E. A. SCHMIDT**¹, F. DESPAS², A. PAVY- LE TRAON^{1,3}, Z. CZOSNYKA³, J. PICKARD^{3,4}, K. RAHMOUNI⁴, A. PATHAK¹, J. SENARD¹

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Abstract: Intracranial pressure (ICP) is the pressure within the cranium. ICP rise compresses brain vessels and reduces cerebral blood delivery. Massive ICP rise leads to cerebral ischemia, but it is also known to produce hypertension, bradycardia and respiratory irregularities due to a sympatho-adrenal mechanism termed Cushing response. One still unresolved question is whether the Cushing response is a non-synaptic acute brainstem ischemic mechanism or part of a larger physiological reflex for arterial blood pressure control and homeostasis regulation. We hypothesize that changes in ICP modulates sympathetic activity. Thus modest ICP increase and decrease were achieved in mice and patients with respectively intra-ventricular and lumbar fluid infusion. Sympathetic activity was gauged directly by microneurography, recording renal sympathetic nerve activity in mice and muscle sympathetic nerve activity in patients, and gauged indirectly in both species by heart-rate variability analysis.

In mice (n=15), renal sympathetic activity increased from 29.9 ± 4.0 bursts.sec-1 (baseline ICP 6.6 ± 0.7 mmHg) to 45.7 ± 6.4 bursts.sec-1 (plateau ICP 38.6 ± 1.0 mmHg) and decreased to 34.8 ± 5.6 bursts.sec-1 (post-infusion ICP 9.1 ± 0.8 mmHg). In patients (n=10), muscle sympathetic activity increased from 51.2 ± 2.5 bursts.min-1 (baseline ICP 8.3 ± 1.0 mmHg) to 66.7 ± 2.9 bursts.min-1 (plateau ICP 25 ± 0.3 mmHg) and decreased to 58.8 ± 2.6 bursts.min-1 (post-infusion ICP 14.8 ± 0.9 mmHg). In patients 7 mmHg ICP rise significantly increases sympathetic activity by 17%. Heart-rate variability analysis demonstrated a significant vagal withdrawal during the ICP rise, in accordance with the microneurography findings. Mice and human results are alike.

We demonstrate in animal and human that ICP is a reversible determinant of efferent

sympathetic outflow, even at relatively low ICP levels. ICP is a biophysical stress related to the forces within the brain. But ICP has also to be considered as a physiological stressor, driving sympathetic activity. The results suggest a novel physiological ICP-mediated sympathetic modulation circuit and the existence of a possible intracranial (i.e. central) baroreflex. Modest ICP rise might participate to the pathophysiology of cardio-metabolic homeostasis imbalance with sympathetic over-activity, and to the pathogenesis of sympathetically-driven diseases.

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Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.10/SS2

Topic: F.07. Autonomic Regulation

Support: DARPA Targeted Neuroplasticity Training (TNT) N66001-17-2-4008

Title: Vagus nerve stimulation modulates respiratory and cardiac function in the common marmoset

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Abstract: Vagus nerve stimulation (VNS) is used clinically to treat epilepsy and depression, and has been proposed as a treatment for tinnitus, inflammatory disorders, heart failure, obesity and stroke rehabilitation, as well as a neuromodulation modality for augmenting learning and memory. Enhancements in learning within sensory, motor, and cognitive systems have been shown primarily in rodent models, with limited data from non-human primates. Such data are crucial for understanding mechanisms of VNS applications in humans, and for validating efficacy and optimizing stimulation parameters.

Here, we have established the first common marmoset (*Callithrix jacchus*) model for a comprehensive study of VNS neuromodulation in non-human primates. Chronic cuff electrodes were implanted around the left cervical vagus nerve, and electrode status was monitored with impedance spectroscopy. Testing of the activation of physiological biomarkers included sweeping the VNS parameter space and analyzing responses in ECG and respiration signals of both anesthetized and awake, head-restrained marmosets. All animals included in the study consistently exhibited breath entrainment immediately after VNS-onset. Over the duration of VNS pulse trains, animals either showed monotonic increases in respiratory rate or breath

amplitude. Thresholds for respiratory effects of VNS were higher in awake than anesthetized conditions. There were no cardiac responses to left cervical VNS except for an increase in heart rate at high intensities. These findings quantify for the first time the respiratory and cardiac effects of VNS in marmosets.

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Poster

069. Recent Advances in Cardiovascular Regulation

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Program #/Poster #: 069.11/SS3

Topic: F.07. Autonomic Regulation

Support: NIH Grant R01 NR-013625
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AHA Grant 17POST33440099 (B.R.)

Title: Regional brain blood flow and diffusion changes in cognition regulatory sites in patients with heart failure

Authors: *B. ROY¹, X. SONG², C. CABRERA-MINO¹, G. C. FONAROW³, M. A. WOO¹, R. KUMAR^{2,4,5,6}

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Abstract: Heart failure (HF) patients show significant brain injury in various cognitive control areas, including the prefrontal cortices, frontal white matter, caudate, and hippocampus. Cognitive dysfunctions associated with brain damage in these areas reduce self-care and increase morbidity and mortality in HF subjects. Reduced cerebral blood flow (CBF), resulting from low cardiac output, may lead to regional brain changes, but such relationships between hemodynamic alterations and brain changes in these specific sites and cognitive symptoms are not examined in HF subjects. Our aim was to determine regional brain CBF changes derived from arterial spin labeling (ASL) and tissue integrity from diffusion tensor imaging (DTI) based mean diffusivity (MD) procedures in cognitive control areas in HF over controls, and evaluate the relationships between cognitive scores and CBF changes in HF subjects. We acquired ASL and DTI images from 19 HF [age, 55.5±9.1 years; BMI, 27.7±5.3 kg/m²; 13 male; LVEF <40%] and 23 controls (age, 51.7±5.3 years; BMI, 25.4±2.9 kg/m²; 16 male) using a 3.0-Tesla magnetic resonance imaging scanner and examined cognition using the Montreal cognitive assessment (MoCA). The CBF and MD maps were normalized to a common space, smoothed, and compared voxel-by-voxel between groups using ANCOVA (covariates: age, gender; SPM12, uncorrected p < 0.005). Significant differences in MoCA scores between groups were evaluated using ANCOVA

(covariates: age and gender). In addition, partial correlations (SPM12; covariates, age, gender; uncorrected threshold $p < 0.005$) were used to examine associations between regional CBF values and MoCA scores in HF subjects. No significant differences in age, gender, or BMI appeared between groups. MoCA scores were significantly lower in HF compared to controls. Multiple brain areas, responsible for cognitive functions, showed reduced CBF and increased MD values in HF over controls, including the prefrontal cortex, hippocampus, and frontal white matter. Significant positive correlations emerged between CBF and MoCA values in the prefrontal cortices, frontal white matter, and caudate in HF subjects. HF patients show significant brain damage and altered CBF in sites associated with cognition regulation. The co-existence of abnormal tissue integrity and reduced CBF suggests that potential cause of brain injury may be compromised CBF. The findings of altered site-specific CBF values correlated with cognitive scores in comparable regions responsible for cognition regulation indicate the need for identification of effective treatments for reducing brain damage by improving cerebrovascular auto-regulation/CBF in HF.

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Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.12/SS4

Topic: F.07. Autonomic Regulation

Title: Intermittent transdermal vagus nerve stimulation increases heart rate variability

Authors: ***R. W. ROOSEVELT**¹, B. HARRIS¹, G. COLLIER²

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Abstract: Transdermal vagus nerve stimulation (tVNS) is a potential approach for treating of a range of disorders including epilepsy, closed head injury, stroke, ADHD, and affective disorders. Evidence supporting the effectiveness of tVNS remains encouraging but tentative. The capacity of tVNS to activate brainstem structures thought to produce the therapeutic effects of VNS has been demonstrated. Additionally, the capacity of tVNS to increase heart rate variability has been demonstrated in several studies. However, in those studies, continuous rather than intermittent tVNS was applied. The continuous stimulation approach is disadvantageous because it is impractical in treatment of human subjects who would be unlikely to tolerate constant stimulation. In comparison, standard VNS, which is invasive requiring surgical implantation of the device, stimulation is applied to the nerve at the carotid level intermittently. Because intermittent stimulation in standard VNS has proven successful in human patients for epilepsy, we hypothesized that intermittent stimulation might also be effective in increasing heart rate

variability **METHODS:** To test the hypothesis that intermittent transdermal stimulation of the auricle branch of the vagus increases heart rate variability we conducted an exploratory study in healthy humans. Vagal stimulation was applied to the ventral and dorsal aspects of the ear at the concha level. Electrical stimulation was 0.5 mA 30 HZ in 15 second trains once every 60 seconds over a ten minute period. Heart rate variability was assessed from EEG recordings obtained during baseline and stimulation. Root Mean Square of the Successive Differences (RMSSD) was calculated for both periods and percent of baseline scores were calculated. **RESULTS:** RMSSD values in the 0.5 mA stimulation group increased to 110% of baseline values. RMSSD for the five responding participants increased to 122% of baseline; whereas the two non-responders decreased to 82% of baseline values. Similar changes were not observed in the control participants. **CONCLUSION:** Results from this exploratory study suggest that intermittent transdermal vagus nerve stimulation may be sufficient to increase heart rate variability. Further study is required to firmly establish optimal stimulation parameters.

Disclosures: **R.W. Roosevelt:** None. **B. Harris:** None. **G. Collier:** None.

Poster

069. Recent Advances in Cardiovascular Regulation

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Program #/Poster #: 069.13/SS5

Topic: F.07. Autonomic Regulation

Support: NIH R01 NR-013930
NIH R01 NR-016463

Title: Assessment of caudate nuclei volumes, cognition, and mood functions in adolescents with single ventricle heart disease

Authors: ***S. NOORANI**¹, **B. ROY**², **S. SINGH**³, **N. HALNON**⁴, **M. WOO**², **A. LEWIS**⁸, **N. PIKE**², **R. KUMAR**^{3,5,6,7}

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Abstract: Adolescents with single ventricle heart disease (SVHD) exhibit mood and cognitive deficits, in addition to autonomic issues. The basal ganglia structures, the caudate nuclei, are implicated in cognitive and mood functions that are significantly impaired in the condition. However, the integrity of the caudate structures in SVHD adolescents is unclear. Our aim was to determine the global caudate nuclei volumes, and evaluate the relationships between caudate volumes and cognitive and mood scores in SVHD and healthy adolescents. We acquired two

high-resolution T1-weighted images from 23 SVHD (age, 15.9±1.3 years; BMI, 21.6±4.9 kg/m²; 14 male) and 37 control subjects (age, 16.0±1.1 years; BMI, 22.7±5.3 kg/m²; 19 male) using a 3.0-Tesla MRI scanner, as well as assessed mood (Patient Health Questionnaire 9, PHQ-9) and memory (Wide Range Assessment of Memory and Learning – Second Edition, WRAML2) functions. Both T1-weighted images were realigned, averaged, bias-corrected, and rigid-body aligned to a common space, and were used for manual outlining left and right caudate. The global caudate volumes were compared between groups using ANCOVA (covariates: age, gender, and head size), and mood and general memory index (GMI) scores were compared between groups using independent samples t-tests. In addition, partial correlations (covariates: age, gender, and head size) were used to examine associations between caudate volumes and cognition and mood scores in SVHD and control subjects. No significant differences in age, gender, or BMI appeared between groups. SVHD subjects showed significantly higher PHQ-9 scores (SVHD vs controls; 8.0±5.5 vs 3.6±2.8; p = 0.001) and significantly reduced GMI scores (82.2 ± 13.3 vs 109.7 ± 11.1; p < 0.001), indicating compromised mood and cognition in SVHD compared to controls. SVHD patients showed significantly reduced caudate volumes (left, 3198.8±490.1 vs 3605.0±480.4 mm³, p<0.004; right, 3162.1±475.4 vs 3504.8±465.9 mm³, p<0.011) over control subjects. Significant negative correlations emerged between caudate volumes with PHQ-9 scores (left, r=-0.40, p=0.007; right, r=-0.28, p=0.04) and positive correlations with GMI scores (left, r=0.33, p=0.01; right, r=0.35, p=0.007) in SVHD and controls. SVHD adolescents patients showed significantly reduced caudate volumes, which may contribute to mood and cognitive deficits found in the condition. The findings suggest brain structural basis for functional deficits in the condition. The pathological mechanisms contributing to caudate volume loss may include developmental and/or hypoxia/ischemia induced processes accompanying the condition.

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Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.14/SS6

Topic: F.07. Autonomic Regulation

Support: JSPS Grant No. 17 K01364

Title: Heartbeat analysis for speedy disease/health detection: The scaling exponents computed by EKG-mDFA serve as a useful bioindex

Authors: *T. YAZAWA

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Abstract: Background: In Crayfish [1a, b] and lobster [2], cardiovascular response represents momentarily varying inner emotional tension. Thus, we challenged to measure animal's internal world or internal drive. Methods: We collected a 2000 beat long-time electrocardiogram (EKG) data. Fluctuation/variation of the heartbeat were characterized by modified detrended fluctuation analysis (mDFA), which computes a scaling exponent (SI) from the heartbeat interval time series. The SI is known to distinguish between normal and abnormal hearts [2]. Results: SI values varied with heart conditions (human EKGs >500). SI=1.0 is basal healthy level [2]. The basal state appeared during 1) happily sitting at waiting lounge of the airport, 2) safely driving a car on the country road without chasing. High SIs (1.2-1.5) are known to associate with unpredictable death [2]. Any excise stress was found to be at risk: A high SI appeared during ergometer exercise (n=75), doing squats (n=50), and lots of walking (n=5). In various occasions, SI decreased to 0.6-0.5: 1) sleeping deeply (0.56), 2) concentrating to write an abstract for a congress (~0.7), 3) enjoying very tasty dishes (0.61), 4) watching Eddie Murphy's touching movie Mr. Church (0.75). Conclusions: SI values varies with heart conditions, e.g., healthy basal or stressful conditions. Our mDFA, a time series analysis, could be a breakthrough in autonomic neuroscience. EKG-mDFA is a novel inquisitive way of science ever made. The heart is the window of the brain. [1a] H Schapker et al. 2002, Comp. Biochem. Physiol. A. pp.397-407. [1b] ZP Shuranova et al. 2006, Evidence for an autonomic nervous system in decapod crustaceans. Int. J. Zool. Res. pp.242-283. [2] T. Yazawa 2015 ASME USA

Disclosures:

Poster

069. Recent Advances in Cardiovascular Regulation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 069.15/SS7

Topic: F.07. Autonomic Regulation

Title: Short-term effect of thermal pain on heart rate variability

Authors: *R. K. GOIT¹, R. KHADKA²

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Abstract: Aim of Investigations: Reactivity of the autonomic nervous system to experimental pain stimuli remains poorly understood. Heart rate variability (HRV) attempts to tease out the relative contributions of sympathetic and parasympathetic activity in the autonomic control of the heart and may therefore be more appropriate to investigate autonomic response to short-term nociceptive stimulation in detail. Methods: Sixty right-handed healthy adults (32 males and 28 females), aged 18-30 years, provided rating of pain intensity and unpleasantness following exposure to thermal pain stimulations and indicated their thresholds for barely noticeable and moderate pain during exposures to decreasing and increasing temperatures. Results: The result

showed an increased in sympathetic-baroreflex activity as indexed by low frequency domain measures and a decrease in parasympathetic activity as indexed by high frequency domain measures of HRV. In time-domain measures, the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) and percentage of consecutive RR intervals that differ by more than 50 msec (pNN50) were significantly less. In Poincare plot, standard deviation perpendicular to line of Poincare plot (SD1) and standard deviation along the line of entity in Poincare plot (SD2) were significantly less. Conclusions: Findings suggest the autonomic nervous system is sensitive to induced short-term thermal pain. HRV is a promising measure of autonomic reactivity to short-term thermal pain.

Disclosures: R.K. Goit: None. R. Khadka: None.

Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 070.01/DP10/SS8

Topic: F.07. Autonomic Regulation

Support: AHA 14SDG18300010

Title: Reduced bone marrow adrenergic receptor signaling is protective against microglia activation *ex vivo* following high fat diet feeding

Authors: *N. AHMARI¹, J. J. LEBOWITZ², D. R. MILLER¹, A. K. GOPINATH¹, R. M. LARKIN¹, N. J. BLAKER¹, W. L. MALPHURS¹, C. J. MARTYNIUK¹, H. KHOSHBOUEI¹, L. F. HAYWARD³, J. ZUBCEVIC⁴

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Abstract: Cardiovascular and metabolic disorders are characterized by elevated immune responses. Chronic increase in bone marrow (BM) sympathetic nerve activity (SNA) heightens the release of inflammatory cells (ICs) into circulation. Conversely, genetic ablation of BM beta-adrenergic receptors reduces circulating tissue-infiltrating ICs, resulting in reduced blood pressure (BP) and dampened microglial activation in the paraventricular nucleus. Here, we hypothesized that SNA-, high fat diet (HFD)-dependent modification of circulating ICs will activate cultured microglia *ex vivo*. BM mouse chimera were generated by irradiation/reconstitution with adrenergic beta 1/ 2 receptor knock out (Adrb1.b2 KO) mice, to generate BM C57-Adrb1.b2 KO chimera characterized by reduced responses of BM to SNA and immunosuppression. Mice were placed on either control (10 kcal fat) or HFD (60 kcal fat) *ad libitum* for ten weeks, and a low subpressor dose of angiotensin II (Ang II) s.c in final four weeks. Flow cytometry quantified circulating ICs (T cells, neutrophils, macrophages). At

endpoint, circulating mononuclear ICs were isolated and co-incubated with ramified serum-free primary mouse microglia for twelve hours at 1:100 ratio of IC to microglia. Microglia were then processed for IHC with anti Iba1 (Wako) and I-A/I-E (Biolegend cat# 107650) to investigate the patterns of activation. Image analysis was carried out in Nikon Elements imaging software (Nikon, Melville NY). The BM C57-Adrb1.b2 KO chimera mice on HFD were protected from total body weight and visceral fat gain compared to BM control chimera ($P < 0.05$ vs control diet). No changes were observed in circulating CD4 T-cells or neutrophils between groups and treatments. However, there was a significant reduction in circulating monocytes and monocyte progenitors, but only in the HFD-fed BM control chimera (~ 62% and 68% reduction respectively vs control diet). *In vitro* co-incubation of microglia with circulating mononuclear ICs derived from HFD-fed BM control chimera decreased microglial processes (total cell area; by 23.9%), processes length (by 10.4%), and total cell perimeter (by 10.63%), and increased microglial cell body size (circularity, by 10%), thus confirming their ability to activate microglia ($P < 0.05$ one way ANOVA). These microglial responses were absent following incubation with mononuclear ICs derived from BM C57-Adrb1.b2 KO chimera on either diet. Therefore, there may be a phenotypical change in BM C57-Adrb1.b2 KO chimera ICs, which are characterized by reduced ability to produce microglial-dependent neuroinflammatory responses.

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Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 070.02/SS9

Topic: F.07. Autonomic Regulation

Support: NIH SPARC Grant OD023848

Title: Characterization of cardiac nerve synaptic transmission in the mouse stellate ganglion

Authors: *J. D. TOMPKINS¹, M. W. DOYLE², M. C. ANDRESEN²

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Abstract: The heart receives substantial sympathetic efferent input from the stellate ganglion (SG). The gross anatomy and organization of the SG varies across species. To leverage genetic approaches, we focused on characterization of synaptic transmission at mouse SG neurons using intracellular recordings. In the mouse, the SG is a fusion of neurons at the cervical-thoracic chain transition with connections rostrally to the superior and middle cervical ganglion and caudally to

the thoracic chain ganglia. C8, T1 and T2 converge directly onto the SG complex. The present studies were directed to the nerve trunk exiting the SG which includes efferent postganglionic axons on their way to the heart - the cardiac nerve (CN). In excised SGs, CN stimulation recorded using sharp microelectrodes or patch pipettes elicited responses with slow conduction velocities, <2 m/s. Graded CN or ventral ansa stimulation activated retrograde action potentials that persisted in hexamethonium (HX). At longer latencies, stimuli recruited unitary synaptic responses (EPSC, EPSP) that were blocked by HX. 84% of neurons (n=30) displayed 1-3 synaptic inputs activated from CN stimuli. The distribution of amplitudes showed a single continuous mode with no evidence of subsets of amplitudes ("big" and "little"). Graded stimulation of preganglionic nerve trunks (e.g. T2) elicited excitatory nicotinic EPSCs similar in all respects to CN synaptics. In some ganglia, simultaneous patch recordings from two neurons allowed examination of recruited synaptics to test for common inputs (diverging/converging). In no case did stimuli activate synaptic inputs to both neurons and depolarization of one neuron did not activate the 2nd neuron supporting fully independent connections. Neurons filled with Neurobiotin uniformly indicated elaborate dendritic trees (5-9 primary dendrites) and responses corresponded to the filled axon exiting a single outflow bundle.

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Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

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Program #/Poster #: 070.03/SS10

Topic: F.07. Autonomic Regulation

Support: Russian Foundation for Basic Research grant #16-04-01122

Title: Development of the reporters for all-optical study of neuro-cardiac transmission

Authors: *O. SHCHERBAKOVA¹, N. A. VERLOV², R. A. PANTINA²

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Abstract: Performance of the mammalian heart is regulated by balance of inputs of sympathetic and parasympathetic nervous system (Armour et al., 1994). Sympathetic neurons are known to release multiple neurotransmitters - epinephrin, nor-epinephrin, acetylcholin, NPY and more. It is very likely, that the differential release is stimulus-dependent. In order to investigate neuro-cardiac transmission, we employed model system of co-cultures of neonatal cardiac myocytes and sympathetic neurons. In our previous work, we have shown that sympathetic neurons form functional connections with neonatal cardiac myocytes in culture. The myocyte membrane

develops into specialized zones that surround contacting axons and contain accumulations of the scaffold and signaling proteins (Shcherbakova O.G. et al, 2007). To examine the differential transmitters release in co-cultures of sympathetic neurons and cardiac myocytes we developed optical reporters for monoamine transporter VMAT2-pHTomato, acetylcholine transporter VAcHT-pHTomato and NPY-pHTomato. Since both cardiac myocytes and sympathetic neurons are electrically-active cells, we choose to employ optical stimulation by *PsChR*, one of the phototaxis receptors in the alga *Platymonas* (*Tetraselmis*) *subcordiformis* (Govorunova et al, 2013). Because of its maximum sensitivity at 445 nm, *PsChR* is the most blue-shifted channelrhodopsin found so far. Therefore, imaging of our red-shifted pHTomato-based reporters will not stimulate the actuator *PsChR* permanently. The lentiviral constructs bearing both actuator *PsChR* and one of the reporters - VMAT2-pHTomato, VAcHT-pHTomato or NPY-pHTomato - will enable quantitative analysis of the different transmitters release in co-cultures of sympathetic neurons and cardiac myocytes. Grant support: Russian Foundation for Basic Research grant #16-04-01122 Armour, J.A., and J.L. Ardell. 1994. Neurocardiology. Oxford University Press, New York, NY. 443 pp. Shcherbakova O.G., Hurt C.M., Xiang Y., Dell'Aqua M., Zhang Qi, Tsien R.W., Kobilka B. Organization of beta-adrenoceptor signaling compartments by sympathetic innervation of cardiac myocytes. The Journal of Cell Biology, 2007, Feb 12; 176(4):521-332007. Govorunova E., Sineshchekov O., Hai Li, Janz R and Spudich J Characterization of a Highly Efficient Blue-shifted Channelrhodopsin from the Marine Alga *Platymonas subcordiformis*. J Biol Chem, 2013 Oct 11;288(41).

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Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.04/SS11

Topic: F.07. Autonomic Regulation

Support: FAPESP Grant #2016/05218-2
CNPq
PADC-FCF/UNESP.

Title: Medial amygdaloid nucleus modulates cardiovascular responses to the emotional stress in rats by the angiotensinergic neurotransmission

Authors: *W. C. FERREIRA, L. GOMES-DE-SOUZA, C. C. CRESTANI
Lab. of Pharmacology, Sch. of Pharmaceut. Sci., São Paulo State Univ., Araraquara, Brazil

Abstract: Circuits in the central nervous system coordinate the physiological responses during aversive situations. A limbic structures implicated in the control of cardiovascular responses to

the stress is the medial amygdaloid nucleus (MeA). Angiotensinergic mechanisms have been described as a mechanism involved in these to the stress. However, the involvement of angiotensin II (ANG II) and angiotensin 1-7 (ANG 1-7) receptors in cardiovascular control in the MeA have never been investigated. Thus, the aim of this study was to investigate the involvement of AT₁ receptor and MAS receptor within the MeA in control of cardiovascular responses evoked by an acute session of restraint stress in rats. For this, male Wistar rats (240g-260g) had cannula-guide bilaterally implanted into the MeA. After seventy-two hours, a catheter was implanted in the femoral artery and 24 hours later mean arterial pressure (MAP) and heart rate (HR) were recordings. The restraint stress was performed by placing the animals in a plastic cylindrical tube for 60 minutes. Independent group of animals received bilateral microinjections into the MeA of the selective AT₁ receptor antagonist losartan (1nmol/100nL), ANG II (0.05nmol/100nL), ANG 1-7 (0.05nmol/100nL), the Mas receptor antagonist A-779 (0.1nmol/100nL) or vehicle (saline, 100nL) 10 min before the onset of the restraint stress session. We observed that bilateral microinjection of losartan into the MeA enhanced the tachycardia evoked by restraint stress ($F_{(1,11)}=5.9$, $P<0.05$), but without affecting the arterial pressure increase ($F_{(1,16)}=0.8$, $P>0.05$). Similarly, bilateral treatment of the MeA with ANG II enhanced restraint-evoked HR increase ($F_{(1,12)}=5.5$, $P<0.05$) without affecting the MAP response ($F_{(1,17)}=0.1$, $P>0.05$). Bilateral microinjection of A-779 into the MeA decreased the tachycardia to restraint stress ($F_{(1,10)}=65.5$, $P<0.0001$), but without affecting the arterial pressure increase ($F_{(1,17)}=0.7$, $P>0.05$). Conversely, bilateral microinjection of ANG 1-7 into the MeA enhanced the tachycardia evoked by restraint stress ($F_{(1,10)}=9.6$, $P<0.02$) without affecting the arterial pressure increase ($F_{(1,17)}=0.1$, $P>0.05$). Our results indicate an inhibitory role of the AT₁ receptor and a facilitatory role of MAS receptor within the MeA in cardiac responses to emotional stress. Besides, ANG II acting via mechanisms other than the AT₁ receptor plays a facilitatory influence on HR response.

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Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.05/SS12

Topic: F.07. Autonomic Regulation

Support: NIH Grant OT2OD023867

Title: Neuromodulatory effects of auricular vagus nerve stimulation on caudomedial neurons in the nucleus tractus solitarius of the rat

Authors: *C. S. HUBBARD^{1,2}, E. BEAUMONT³, R. SCLOCCO⁴, R. G. GARCIA⁴, C. JUNG⁴, V. NAPADOW⁴, I. AY⁴

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Abstract: The vagus nerve is critically involved in autonomic control and homeostatic balance of cardiovascular, respiratory, and gastrointestinal (GI) function via primary afferents to the nucleus tractus solitarius (NTS), and motor efferents from the nucleus ambiguus and dorsal motor nucleus. Emerging therapies utilizing neuromodulatory technology to target aberrant brainstem vagal circuitry in a myriad of cardiovascular and chronic pain disease states have been developed, including surgical implantation of vagus nerve stimulation (VNS) devices, and more recently, non-invasive transcutaneous VNS (tVNS) via the auricular branch of the vagus nerve (AVBN). The latter approach is especially appealing as it mitigates surgical risks and targets vagal afferents innervating the conchae of the external ear, thereby avoiding vagal efferent-mediated off target effects. However, the exact mechanism mediating auricular tVNS therapeutic action remains unclear, but may involve modulation of NTS neurons receiving primary auricular vagal input. Therefore, the purpose of the present study is to functionally map the AVBN-brainstem-autonomic outflow pathway in rodents using extracellular recordings of caudomedial NTS neurons in response to auricular tVNS. High impedance tungsten electrodes were stereotaxically placed in the caudal NTS, just lateral to the midline, in α -chloralose anesthetized Wistar rats. Activity of single NTS neurons was recorded 5 min prior to, during, and 5 min after AVBN stimulation (5 stimulus trains delivered at 20 Hz with a current intensity of 1 mA and 0.5 ms pulse widths; 15 s ON, 45 s OFF). Captured raw data from each experiment were sampled at 20 kHz (Micro1401, Cambridge Electronic Design; CED), amplified and bandpass filtered (0.1-3 kHz). Spike identification, counting and sorting were conducted using Spike 2 software (version 9; CED). Our initial findings revealed AVBN stimulation elicited differential response patterns in NTS neurons, with the majority of recorded units showing decreased or no change in NTS activity, whereas a small subset displayed an increased discharge rate following AVBN stimulation. Varying intensity and/or frequency of stimulation could modify this recruitment pattern and will need to be investigated. Although preliminary, our findings offer new insights into the functional organization of the AVBN-brainstem-autonomic outflow pathway and will lay the groundwork for testing the fidelity of non-invasive neuromodulatory techniques such as auricular tVNS to mitigate surrogate markers of clinical symptoms in animal disease models of chronic pain, GI, and cardiovascular function.

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Poster

070. Cardiovascular Regulation: New Insights

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Topic: F.07. Autonomic Regulation

Support: National Research Foundation of Korea, funded by the Ministry of Science, ICT, and Future Planning (2011-0018358)

Title: Tentonin 3/TMEM150c, a mechanosensitive channel, is essential for the baroreceptor reflex

Authors: *G. HONG¹, U. OH², H. KIM³, H. KIM³

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Abstract: Arterial baroreceptors are stretch receptors detecting blood pressure changes in the large arteries. Because of the pressure change, mechanosensitive channels in baroreceptors are responsible for the detection of pressure change. Previously, some candidate channels were introduced for possible role in the mechanotransduction in baroreceptors. TTN3 is a cation channel activated by mechanical strokes on the cell surface when expressed heterologously. It is grouped to be a new class because it elicits slow inactivation kinetics, stark comparison with Piezo1 and 2 that show rapid inactivation kinetics. As TTN3 is a mechanosensitive channel, we assumed that TTN3 acts as a mechanosensitive channel responsible for baroreceptor reflex. Indeed, we found that TTN3 is expressed in nodose ganglion (NG) neurons that innervate in aortic baroreceptors and in nerve terminals of aortic depressor nerves. Application of mechanical steps to cultured NG neurons elicited slowly adapting (SA) currents, which was absent in NG neurons of TTN3^{-/-} mice. Neural activity of aortic depressor nerves from TTN3^{-/-} mice in response to pressure in the isolated aorta is markedly lower than that of the wild-type (WT) mice. More importantly, continuous recording for 24 hours of blood pressure and heart rate were made with freely moving mice of both genotypes. As expected for baroreceptor block, TTN3^{-/-} mice showed hypertension, tachycardia, and unstable blood pressure. The sensitivity of baroreceptor reflex was markedly lower in TTN3^{-/-} mice. For rescue experiments, we overexpressed TTN3 in nodose ganglia after injection of viral vectors expressing *Ttn3*. The *Ttn3*-overexpressed mice showed a reversal of blood pressure, heart rate, and baroreceptor reflex sensitivity to those of WT mice. These results clearly indicate that TTN3 is a molecular determinant contributing to dynamic change in mechanosensitivity in baroreceptors.

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Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.07/SS14

Topic: F.07. Autonomic Regulation

Support: NIH Grant DC013788

Title: Responses of neurons in the rostral ventrolateral medulla (RVLM) to anticipated, passive, and active movement

Authors: D. M. MILLER¹, A. JOSHI¹, J. P. BIELANIN¹, S. R. WITTMAN¹, A. A. MCCALL¹, S. M. BARMAN², *B. J. YATES¹

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Abstract: It is well established that RVLM neurons play a key role in controlling sympathetic nervous system activity and blood pressure. However, the activity of these neurons has mainly been studied in decerebrate or anesthetized animals. In this study, we examined in conscious adult female cats the activity of RVLM neurons that were identified by their location and changes in firing rate correlated with the cardiac cycle (cardiac-related activity, CRA). We recorded the activity of the neurons during 40° head-up tilts that were preceded by a light cue, such that the animals anticipated the rotations. The CRA of the units varied during the recording session, and changes in heart rate and unit activity were not related, indicating that the responses of RVLM neurons to baroreceptor inputs were modulated by other signals. The firing rate of only a subset of neurons was affected by 40° tilts, and the activity of the units did not change following the light cue and prior to tilts. However, during spontaneous movements detected through EMG recordings, a number of RVLM neurons exhibited increased activity, sometimes beginning prior to the onset of muscle contraction. These data suggest that RVLM neurons in conscious animals integrate a variety of signals, including those from baroreceptors and higher centers, and that they are highly engaged in adjusting blood pressure during active movements.

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Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.08/TT1

Topic: F.07. Autonomic Regulation

Support: Deutsches Zentrum für Herz-Kreislaufforschung (DZHK, FKZ: 81X2710149)

Title: Deletion of Trip8b alters modulation of cardiac electrophysiology by intracardiac neurons

Authors: *K. SCHERSCHEL¹, C. JUNGEN¹, N. ERLINHARDT², C. EICKHOLT¹, D. M. CHETKOVICH³, N. KLOECKER⁴, C. MEYER¹

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Abstract: The neuron-specific tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b/PEX5R) is an auxiliary subunit of hyperpolarization-activated cation (HCN) channels known to limit their cyclic nucleotide gating in the central nervous system. A dense network of intracardiac neurons has been shown to be relevant for cardiac electrophysiology but understanding of underlying mechanisms is limited. The aim of this explorative study was to investigate the influence of intracardiac neurons on the electrophysiology of the heart in a Trip8b-deficient (KO) mouse model.

Ex vivo electrophysiological characterisation was performed in a whole heart Langendorff model with male Trip8b/PEX5R-deficient mice (C57Bl6 background, aged 12-22 weeks, n=6) using programmed stimulation. Wildtype (WT) littermates served as controls. No significant differences in baseline heart rate could be detected between genotypes (528.3±24.42 ms in WT vs 503.3±10.22 ms in KO). However, atrial refractory period was increased in KO animals from 25.0±2.2 ms to 32.7±2.2 ms (p=0.033), the atrioventricular nodal recovery interval was prolonged from 59.0±3.5 ms to 73.7±4.4 ms (p=0.026), and Wenckebach periodicity increased from 71.7±2.0 ms to 81.2±3.8 ms (p=0.044). Ganglionic blockade by systemic perfusion with 0.5 mM hexamethonium reversed these effects. Trip8b/PEX5R immunoreactivity was found in intracardiac neurons, but as expected not in the sinoatrial node or the myocardium of WT mice. In good agreement, we also observed HCN1 and HCN2 immunoreactivity in intracardiac neurons.

In conclusion, modulation of cardiac electrophysiology by intracardiac neurons involves the HCN channel auxiliary subunit Trip8b/PEX5R. Whether and how Trip8b/PEX5R controls activation of HCN channels in intracardiac neurons and thus parasympathetic tone needs to be elucidated in further studies.

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Poster

070. Cardiovascular Regulation: New Insights

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Topic: F.07. Autonomic Regulation

Support: Conacyt Grant No. 252702

Title: Effect of chronic administration of sodium hydrosulfide, L-cysteine and DL-propargylglycine on the the cardiovascular changes induced by a high fat diet in rats

Authors: *S. HUERTA, C. B. GOMEZ, G. MENÉNDEZ-REVILLA, A. SANCHEZ-LOPEZ, D. CENTURIÓN

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Abstract: Obesity is an abnormal fat accumulation associated with cardiovascular diseases such as hypertension, among other disorders. It has been observed that, during obesity and hypertension, H₂S biosynthesis and plasma levels of H₂S are significantly reduced. As previously reported, H₂S is capable of inducing vasodilation as well as inhibition of the sympathetic nervous system. In this respect, this study was designed to evaluate the effects of a chronic treatment with Sodium Hydrosulfide (NaHS), L-cysteine (L-Cys) and DL-Propargylglycine on the haemodynamic changes as well as the sympathetic tone in a high-fat diet (HFD) model of obesity in Wistar male rats. For this purpose, Wistar rats received normal fat diet (NFD, n=6) or high-fat diet (HFD; n=30) for 12 weeks. Then, the HFD rats were divided into 5 subgroups (n=6 each) which received daily i.p. injections during 4 weeks of: (1) nothing; (2) vehicle (PBS, 1 ml/kg); (3) NaHS (5.6 mg/kg); (4) L-Cys (300 mg/kg); (5) DL-PAG (1 mg/kg). Blood pressure was measured by plethysmograph method before (week 12) and after (week 16) each treatment. The cardiovascular function was evaluated in pithed rats by determining the vasopressor responses induced by selective stimulation of the vasopressor sympathetic outflow and i.v. bolus of noradrenaline (endogenous ligand), methoxamine (α_1 -adrenoceptor agonist) and UK 14304 (α_2 -adrenoceptor agonist); as well as tachycardic responses induced by noradrenaline (endogenous ligand). HFD significantly increased haemodynamic variables compared to NFD. Interestingly, NaHS treatment significantly diminished those values to basal after 4 weeks of chronic treatment while L-Cys and DL-PPG induced a slight decrease in haemodynamic variables. On the other hand, in pithed rats, HFD enhanced the vasopressor responses induced by sympathetic stimulation and methoxamine compared to NFD. Chronic administration of NaHS and L-Cys significantly decreased these responses when compared to vehicle. Lastly, high-fat diet-induced an increase in tachycardic responses induced by noradrenaline when compared to

normal fat diet. Surprisingly, vehicle induced a decrease in those responses compared to HFD control. Furthermore, chronic treatment with L-Cys significantly decreased the tachycardic responses induced by noradrenaline while chronic treatment with NaHS and DL-PAG failed to affect these responses. Taken together, we concluded that chronic treatment with NaHS and L-Cys are effective in ameliorating the cardiovascular changes induced by obesity.

Disclosures: S. Huerta: None. C.B. Gomez: None. G. Menéndez-Revilla: None. A. Sanchez-Lopez: None. D. Centurión: None.

Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 070.10/TT3

Topic: F.07. Autonomic Regulation

Support: FAPESP #2016/05028-9
PADC-FCF/UNESP

Title: Role of GABAergic receptors in the lateral hypothalamus in cardiovascular responses during acute restraint stress in rats

Authors: *L. GOMES-DE-SOUZA, R. BENINI, W. COSTA-FERREIRA, C. C. CRESTANI
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Abstract: Introduction: The lateral hypothalamus (LH) has been described as one of the hypothalamic areas that is involved in the behavioral and physiological responses triggered by aversive stimuli. Previous studies indicated an inhibitory influence of the LH on the tachycardia response caused by acute restraint stress, without affecting the increase of arterial pressure.

However, the role of GABAergic neurotransmission within the LH in cardiovascular responses evoked by aversive stimuli has not been investigated. **Objectives:** We investigated the effect of bilateral microinjection into the LH of selective antagonists of either GABA_A or GABA_B receptor in cardiovascular responses induced by an acute session of restraint stress in rats.

Materials and Methods: Male Wistar rats (250g) had cannula-guide bilaterally implanted within the LH. A catheter was implanted in the femoral artery for mean arterial pressure (MAP) and heart rate (HR) recording. The response of reduction in tail skin temperature was measured by a thermovisor as an index of sympathetic-mediated vasoconstriction response. The restraint stress was realized by placing the animals in a plastic cylindrical tube for 60 minutes.

Independent groups of animals received bilateral microinjection into the LH of the selective GABA_A receptor antagonist SR95531 (0.1nmol/100nL), the selective GABA_B receptor antagonist CGP3538 (10nmol/100nL) or vehicle (saline, 100nL) 10 minutes before the onset of the restraint session. **Results:** Bilateral microinjection of SR95531 into the LH did not alter the

increase on MAP ($F_{(1,15)}=0.007$, $P>0.05$) and the drop in tail skin temperature ($F_{(1,15)}=0.009$, $P>0.05$). However, the blockade of the GABA_A receptor within the LH decreased the restraint-evoked tachycardiac response ($F_{(1,15)}=4.776$, $P<0.05$). Bilateral microinjection of CGP3538 into the LH did not alter the restraint-evoked increase on MAP ($F_{(1,12)}=0.010$, $P>0.05$) and HR ($F_{(1,12)}=0.010$, $P>0.05$), as well as the drop in tail skin temperature ($F_{(1,12)}=7.181$, $P>0.05$).

Conclusion: The GABAergic neurotransmission in the LH, acting through activation of the GABA_A receptors, is involved in tachycardiac response during aversive threats.

Disclosures: L. Gomes-de-Souza: None. R. Benini: None. W. Costa-Ferreira: None. C.C. Crestani: None.

Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.11/TT4

Topic: F.07. Autonomic Regulation

Support: NIH Grant R00HL125805

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NIH Grant R01HL139868

HI Grant R01HL136595

Title: Identifying ‘angiotensin sensitive’ neurons in the lamina terminalis that coordinate endocrine, autonomic and behavioral responses mediating cardiovascular homeostasis

Authors: *A. D. DE KLOET¹, A. R. ALLEYNE², S. W. HARDEN², E. B. BRUCE¹, K. M. CAHILL², Y. TAN², M. K. RAIZADA¹, C. SUMNERS¹, C. J. FRAZIER², E. G. KRAUSE²

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Abstract: Angiotensin type 1a receptors (AT1a) within the CNS elevate blood pressure by influencing sympathetic outflow and vasopressin (VP) secretion; however, the neuronal circuits mediating these effects remain unclear. The present studies characterize the structure and function of AT1a neurons residing in the median preoptic nucleus (MnPO) and the organum vasculosum of the lamina terminalis (OVLT), thereby evaluating their potential role in blood pressure control. Using male AT1a-Cre mice, initial studies combined genetic reporting with *in situ* hybridization to reveal that AT1a neurons in the MnPO and OVLT are largely excitatory ($87\pm 4\%$ express vesicular glutamate transporter 2). Subsequently, AT1a-Cre mice were delivered a Cre-inducible adeno-associated virus to induce expression of channelrhodopsin-2 (ChR2) and enhanced yellow fluorescent protein (eYFP) specifically within AT1a neurons of the MnPO/OVLT (AAV-ChR2-eYFP). Control mice were delivered AAV-eYFP. Analysis of eYFP

immunofluorescence revealed that neurons within the MnPO/OVLT that express AT1a send projections to the paraventricular nucleus of the hypothalamus (PVN) that appear to synapse onto VP synthesizing neurons. To evaluate the functionality of this connection, we optogenetically stimulated AT1a neurons in the region while recording cardiovascular parameters in anesthetized mice. Ten-minutes of optogenetic stimulation (473 nM; 15 Hz; 20 ms pulse width; 60 s ON; 60 s OFF) robustly elevated systolic blood pressure in AAV-ChR2-eYFP mice relative to AAV-eYFP controls. This effect was rapid in its onset, but persisted for the entire 50 min of cardiovascular recording. Intriguingly, the optogenetic stimulation also resulted in increased Fos induction in AVP neurons within the PVN relative to AAV-eYFP controls. Lastly, optogenetic stimulation of these neurons in conscious freely-moving mice significantly increased both water and 0.3M NaCl consumption, while their inhibition had the opposite effect. Collectively, these results suggest that excitation of AT1a neurons in the MnPO/OVLT recruits autonomic, neuroendocrine and behavioral responses that promote robust and sustained increases in blood pressure.

Disclosures: A.D. de Kloet: None. A.R. Alleyne: None. S.W. Harden: None. E.B. Bruce: None. K.M. Cahill: None. Y. Tan: None. M.K. Raizada: None. C. Sumners: None. C.J. Frazier: None. E.G. Krause: None.

Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 070.12/TT5

Topic: F.07. Autonomic Regulation

Support: HL 135498

Title: Tumor necrosis factor alpha receptor 1 in the hypothalamic paraventricular nucleus contributes to reactive oxygen production and glutamate signaling under basal and hypertensive states

Authors: *M. J. GLASS, G. WANG
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Abstract: Tumor necrosis factor alpha (TNF α) has been implicated in blood pressure regulation and hypertension, however, the mechanisms subserving these actions have not been fully elucidated. Using a multidisciplinary strategy, we provide evidence that TNF α type 1 receptor (TNFR1) is positioned for the modulation of established hypertension-associated signaling pathways involving reactive oxygen species (ROS) production and glutamate signaling in the paraventricular hypothalamic nucleus (PVN), a critical central coordinator of cardiovascular function. Using high-resolution immunoelectron microscopy (iEM) we report that TNFR1 has a

diverse cellular expression in the PVN, but is predominantly found in neurons. Over 80% of TNFR1-labeled profiles are neuronal, and among neuronal profiles approximately 80% are dendrites. By dual labeling iEM, we also show that TNFR1 is expressed in sympathoexcitatory PVN neurons retrogradely labeled from the spinal cord (~70%). However, there is a lower degree of PVN co-expression of TNFR1 with the neuroendocrine marker arginine vasopressin (~20%). At the signaling level, *in situ* dihydroethidium microfluorographic analysis demonstrates that TNF α application stimulates ROS production in dissociated PVN neurons. This action is inhibited by local TNFR1 spatial-temporal knockdown. In addition, by whole-cell patch-clamping, TNF α is shown to potentiate NMDA receptor-mediated currents in PVN slices, an effect that is inhibited in TNFR1 knock-out mice. Following an increase of blood pressure in response to 14-day slow-pressor angiotensin II (AngII) administration there is an increase in TNFR1 labeling in presumably functional sites on the plasma membrane of dendritic profiles of PVN neurons. In addition, in dissociated PVN neurons from mice treated with AngII, either TNF α or NMDA application produces a potentiation of ROS production that is blocked in TNFR1 knockout mice. In summary, these results indicate that TNFR1 activation is an important modulator of signaling by ROS and by NMDA receptors in PVN neurons, which may contribute to normal and elevated blood pressure.

Disclosures: M.J. Glass: None. G. Wang: None.

Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

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Program #/Poster #: 070.13/TT6

Topic: F.07. Autonomic Regulation

Support: NIH Grant MH099505

Title: Pharmacological activation of superior colliculus and periaqueductal gray alters physiological measures of arousal

Authors: *C. ELORETTE¹, P. A. FORCELLI², L. MALKOVA²

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Abstract: The superior colliculus (SC) and periaqueductal gray (PAG) are regions mediating response to threat. In both rodents and primates, experimental activation of SC or PAG produces defensive behaviors, even in the absence of fear-inducing stimuli (Forcelli et al. 2017). Furthermore, lesions of SC in primates abolish fearful response to ethological threats (Maior et al. 2011).

Autonomic arousal can be used as a physiological indicator of emotional arousal of an animal responding to a perceived threat. Consistent with this, rodent studies show that activation of SC

or PAG results in changes to heart rate and blood pressure, coordinating behavioral and autonomic responses. The impact of these areas on autonomic arousal in primates is unknown. Here we tested the hypothesis that pharmacological activation of the SC or PAG would alter heart rate and blood pressure in the absence of any additional stimuli. Our pharmacological approach using reversible activation by intracerebral drug microinfusions allows for precise targeting of a neural structure in an awake, behaving animal.

In two male rhesus macaques, we used a telemetry implant (Data Sciences International, St. Paul MN) to measure blood pressure, which also provides an indirect measure of heart rate. We aimed to activate four sites within the SC and two sites within the PAG by unilateral microinjections of bicuculline methiodide (BMI), a GABA_A antagonist (2.5-5 nmol), or saline. This BMI dose is sub threshold to evoke any changes in behavior (Desjardin et al. 2013).

We compared physiological measures thirty minutes post-infusion to baseline. Activation of the superficial and intermediate layers of SC with BMI decreased heart rate (mean difference of 16.3 BPM) and increased blood pressure (mean difference of 0.95 mmHg), while the same dose aimed at the deep layers only increased blood pressure (mean difference of 1.12 mmHg) without changing heart rate. Activation of the PAG decreased heart rate (mean difference of 50.2 BPM) and increased blood pressure (mean difference of 0.61 mmHg) and induced fearful vocalizations. These results indicate that sites within the topography of SC and PAG differentially influence autonomic measures of arousal, a finding similar to those in rodents.

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Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 070.14/TT7

Topic: F.07. Autonomic Regulation

Support: UCF institutional fund to Dr. Zixi (Jack) Cheng

Title: Effects of chronic intermittent hypoxia (cih) on baroreflex control of heart rate (hr) in mice: Aortic depressor afferent, vagal efferent, and central components

Authors: *Z. CHENG¹, J. CHEN¹, H. GU¹, R. D. WURSTER²

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Abstract: Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder that is associated with many cardiovascular complications, such as autonomic dysfunctions, stroke and heart failure. Chronic intermittent hypoxia (CIH) is a prominent feature of OSA. In CIH exposed rodents (a model for OSA), CIH induces similar cardiovascular complications as seen in OSA

patients. In particular, OSA impairs baroreflex control of the heart rate (HR), which is used as an independent indicator for heart failure. The baroreflex control arc includes the aortic depressor nerve (ADN), vagal efferent and central components, therefore we hypothesize that CIH induces dysfunctions of all three components. Since mice can be genetically manipulated, an understanding of the effects of CIH on multiple neural components in the baroreflex arc in wild type mice may lead to future studies of treatments. In this study, we have examined the effects of CIH on baroreceptor afferent, central and vagal efferent components of the baroreflex circuitry in normal wild type C57BL/6J mice. Mice (4-5 months) were exposed to room air (RA) or CIH for 35-50 days and were then anesthetized with isoflurane, ventilated and catheterized for measurement of mean arterial blood pressure (MAP) and HR. Baroreceptor function was characterized by measuring percent changes of integrated ADN activity (Int ADNA) relative to the baseline value in response to the vasodilator sodium nitroprusside and the vasoconstrictor phenylephrine-induced changes in MAP. Data were fitted to a sigmoid logistic function curve. HR responses to electrical stimulation of the left ADN and the right vagus nerve were assessed under anesthesia. Compared with RA controls, CIH significantly increased maximum baroreceptor gain or maximum slope, maximum Int ADNA, and Int ADNA range (maximum-minimum Int ADNA). In addition, CIH increased the maximum amplitude of the bradycardic response to vagal efferent stimulation. In contrast, CIH significantly reduced the maximum amplitude of bradycardic response to left ADN stimulation. Thus, CIH decreased central mediation of the baroreflex but augmented the baroreceptor afferent function and vagal efferent control of HR in mice, which are consistent with the findings in F344 rats.

Disclosures: Z. Cheng: None. J. Chen: None. H. Gu: None. R.D. Wurster: None.

Poster

070. Cardiovascular Regulation: New Insights

Location: SDCC Halls B-H

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Program #/Poster #: 070.15/TT8

Topic: F.07. Autonomic Regulation

Support: NIH/NHLBI (HL093178)
COBRE (P30GM106392)

Title: Deletion of ADAM17 reduces PVN-neuronal excitability and preserves ACE2 compensatory activity in hypertension

Authors: *S. MUKERJEE¹, H. GAO³, T. BASTING², A. ZSOMBOK³, E. LAZARTIGUES²
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Abstract: Brain ADAM17 has previously been shown to contribute to neurogenic hypertension by shedding angiotensin converting enzyme 2 (ACE2) from the cell membrane compromising

the compensatory arm of the renin-angiotensin system (RAS). Our aim is to identify, how ADAM17 and ACE2 impact excitability of pre-sympathetic neurons in the paraventricular nucleus (PVN), leading to long term changes in blood pressure (BP) in drug resistant hypertension.

To address the consequence of lack of ACE2 on neuronal excitability, we used 2 mouse- models, to globally (ACE2-G) or specifically (ACE2-N) delete ACE2 from neurons. A GFP-tagged PRV152 virus was used to identify PVN pre-sympathetic neurons projecting to the kidney. Within 110 h kidney related pre-sympathetic neurons were identified in the PVN, to perform electrophysiological characterization. In normotensive conditions, there were no differences in EPSC within these groups. However, there was a reduced frequency of mIPSC in ACE2-G and ACE2-N mice compared to controls (CON: 1.5 ± 0.3 Hz, n=9; ACE2-G, 0.6 ± 0.1 Hz, n=12; ACE2-N, 0.8 ± 0.2 Hz, n=15; ANOVA, $p < 0.05$), indicating that ACE2 deletion might make these neurons prone to hyperexcitability.

We then investigated the consequence of activating BP-relevant PVN neurons in the presence or absence of ADAM17. SAT mice lacking ADAM17 on PVN neurons were developed by breeding Single minded 1 (Sim1)-cre mice with ADAM17 floxed animals. Deletion was evidenced using a tdTomato reporter. Activation (20 Hz, 10s light pulse) of Sim1-PVN neurons with cre-driven channelrhodopsin, led to increased BP, measured with radiotelemetry (≈ 8 mmHg). Ganglionic blockade prevented this rise, confirming the sympathetic origin of this effect. tdTomato labeled neurons were isolated using cell sorting, followed by qRT-PCR. A 4-fold drop in ADAM17 expression verified ADAM17 deletion (n=4, t test, $p < 0.05$). Reduction in neuronal activation was confirmed by a 4-fold decrease of Fosb expression in SAT mice (n=4, t test, $p < 0.05$). Interestingly, development of DOCA-salt hypertension led to 6-fold increased expression of compensatory ACE2 in the hypothalamus of SAT mice compared to controls (n=4-7, t test, $p < 0.05$) and injecting Ang-II directly in the PVN of normotensive SAT mice, prevented the typical BP increase (CON: 16.6 ± 1.9 , SAT: -0.4 ± 1.3 mmHg, n=3, t test, $p < 0.01$). Deleting ACE2 makes the PVN hyper excitable and knocking out neuronal ADAM17 in the PVN upregulates compensatory ACE2. This prevents Ang II mediated BP increase. Considering, ADAM17-induced shed ACE2 activity in CSF is correlated with systolic BP in hypertensive patients, it brings ADAM17 to the forefront as an antihypertensive drug target.

Disclosures: S. Mukerjee: None. H. Gao: None. T. Basting: None. A. Zsombok: None. E. Lazartigues: None.

Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.16/TT9

Topic: F.07. Autonomic Regulation

Support: NIH HL-119380

Nova Southeastern University Health Professions Division

NIH HL-121456

NIH AG0049450

TL-1 TR001431

UL1-TR001409

Title: Effect of ovariectomy on hippocampal BDNF gene methylation and mRNA expression in Dahl salt-sensitive hypertensive and Dahl salt-resistant rats

Authors: ***R. C. SPETH**^{1,2}, H. W. PANG³, A. LINARES³, N. ROSE³, A. PAI⁴, A. A. DE SOUZA⁴, C. A. WEST⁴, H. JI⁴, M. S. TRIVEDI³, K. SANDBERG⁴

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Abstract: Women's resistance to hypertension and cardiovascular disease prior to, but not after menopause, arises from ovarian hormones. Post-menopausal, women are more susceptible to cognitive impairment and dementias and this risk is higher with premenopausal oophorectomy or premature ovarian failure. We and others have previously reported a substantial increase in blood pressure in Dahl salt-sensitive (DS) rats compared to Dahl salt-resistant (DR) rats, however, forebrain AT1 receptor binding is higher in the DR rats compared to the DS rats regardless of hormonal status in our hands. Brain-derived Neuronal Growth Factor (BDNF) is an indicator of neuronal plasticity and this study examined BDNF mRNA in the hippocampus as a surrogate for cognitive performance in these two rat strains, with and without ovariectomy. In addition, we also measured CpG methylation using bisulfite conversion followed by pyrosequencing in the BDNF gene for epigenetic changes, since such epigenetic regulation can affect BDNF gene expression. We observed a significant ($p < 0.01$) increase in the BDNF mRNA levels in the hypertensive DS rat hippocampus compared to that of the normotensive DR rat. In parallel, there was significant decrease in the CpG methylation levels at (CpG -35, 35 and 43) in the hypertensive DS rats as compared to the DR rat. There was also a significant ($p < 0.01$) decrease in BDNF mRNA in the hippocampus of the ovariectomized rats. These mRNA levels were accompanied by underlying changes in CpG methylation (CpG -35, 35 and 43) in the DS ovariectomized rats. In addition, there was a significant interaction, with ovariectomized DR rats showing a greater reduction in BDNF mRNA than the DS rats. These data are consistent with the hypothesis that loss of ovarian steroid hormones is associated with a reduction in hippocampal neuroplasticity with underlying changes in the BDNF levels as evidenced by the reduction in hippocampal BDNF mRNA expression. This could explain why women who undergo premature menopause are at greater risk of cognitive impairment.

Disclosures: **R.C. Speth:** None. **H.W. Pang:** None. **A. Linares:** None. **N. Rose:** None. **A. Pai:** None. **A.A. de Souza:** None. **C.A. West:** None. **H. Ji:** None. **M.S. Trivedi:** None. **K. Sandberg:** None.

Poster

070. Cardiovascular Regulation: New Insights

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Program #/Poster #: 070.17/TT10

Topic: F.07. Autonomic Regulation

Support: NIH Grant R01 DK056132
NIH Grant T32 GM118292

Title: Fibroblast growth factor 19 alters excitability in the dorsal motor nucleus of the vagus

Authors: *J. WEAN¹, B. N. SMITH²

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Abstract: According to the CDC, there are more than 30 million Americans living with diabetes. Most diabetes research focuses on defects in insulin and glucose metabolism, but emerging evidence suggests that the brain plays an underappreciated role in systemic glucose regulation. One such homeostatic regulatory center is the brainstem dorsal vagal complex (DVC) which monitors metabolic status through both vagal afferent neural and humoral signals including glucose, insulin, and leptin. Parasympathetic motor neurons in the DVC respond to this information by altering vagal output to regulate pancreatic hormone release and hepatic glucose production. Fibroblast growth factor 19 (FGF19) has potent, insulin-independent antidiabetic effects when injected intracerebroventricularly, though the mechanisms of action are unknown. This information, together with the fact that FGF19's receptor/co-receptor combination is present in the DVC, suggests that this area is a prime candidate for the observed antidiabetic effects. Here, patch-clamp electrophysiology was used to measure the effects of FGF19 on action potential (AP) frequency and synaptic currents in vagal motor (i.e., DMV) neurons in brainstem slices from mice. Application of FGF19 (230 pM) either increased (33%), decreased (44%) or caused no change in AP firing in DMV neurons. The frequency of spontaneous synaptic currents was also altered, and FGF19 also caused significant outward or inward whole-cell currents in most DMV neurons. Evidence that FGF19 alters a rectifying potassium current in DMV neurons is under investigation. These cellular effects are consistent with the hypothesis that FGF19 modifies parasympathetic output to the viscera and could contribute to the peptide's effects on metabolism. Studies aimed at understanding anti-diabetic effects of FGF19 in the DVC are underway.

Disclosures: J. Wean: None. B.N. Smith: None.

Poster

071. Thermoregulation: Cool News and Hot Topics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 071.01/TT11

Topic: F.07. Autonomic Regulation

Title: Control of autonomic function by insulin receptors

Authors: *U. HYUN, J.-W. SOHN

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Abstract: It is now well known that insulin affects central nervous system (CNS) neurons to control energy balance and glucose homeostasis. However, it remains incompletely understood how insulin and its cognate receptors affect autonomic neurons and function. In this study, we aimed to delineate acute effects and underlying mechanisms of insulin action on autonomic neurons and identify physiological function of insulin receptors expressed by autonomic neurons. To this end, we utilized the ChAT-IRES-Cre mouse model, which can target cholinergic preganglionic neurons of both sympathetic and parasympathetic nervous systems. Using patch clamp recordings, we found that insulin inhibits identified parasympathetic preganglionic neurons within the dorsal motor nucleus of vagus nerve (DMV). We further characterized acute effects of insulin on synaptic currents onto these neurons.

On the other hand, insulin did not change activity of identified sympathetic preganglionic neurons within the intermediolateral nucleus (IML) of spinal cord. We also characterized several homeostatic parameters including glucose tolerance using a mouse model lacking insulin receptors only in cholinergic neurons. Results from our studies should help to further our understanding of insulin action on autonomic nervous system and post-prandial physiology.

Disclosures: U. Hyun: None. J. Sohn: None.

Poster

071. Thermoregulation: Cool News and Hot Topics

Location: SDCC Halls B-H

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Program #/Poster #: 071.02/TT12

Topic: F.07. Autonomic Regulation

Support: American Diabetes Association
NARSAD

FPWR
JPB Foundation

Title: Dorsal raphe nucleus GABA neurons regulating energy expenditure

Authors: ***A. R. NECTOW**¹, M. SCHNEEBERGER PANE², L. PAROLARI³, V. BHAVE⁴, T. D. BANERJEE⁴, P. WANG³, P. COHEN³, N. RENIER⁵, J. FRIEDMAN⁶

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⁶Rockefeller Univ/ HHMI, New York, NY

Abstract: The central regulation of energy expenditure is critical for survival. Energy expenditure is regulated at both the autonomic and behavioral levels, respectively through adaptive thermogenesis and locomotor activity. These processes are thought to be regulated by neurons within the hypothalamus and brainstem, though the latter cell types are less well understood. We have recently identified a population of GABAergic neurons within the brainstem's dorsal raphe nucleus (DRN) that are critical for regulating appetite. We have recently found that these so-called DRN Vgat neurons are also activated by ambient warmth and polysynaptically innervate interscapular brown adipose tissue (iBAT). Furthermore, these neurons can potently and bidirectionally dissipate energy through both behavioral and autonomic mechanisms. Whole-brain mapping has established that these neurons are also, surprisingly, broadly projecting and terminate in numerous loci implicated in the regulation of energy expenditure. Together, this work establishes DRN Vgat neurons as a critical mediator of energy homeostasis.

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Poster

071. Thermoregulation: Cool News and Hot Topics

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Program #/Poster #: 071.03/TT13

Topic: F.07. Autonomic Regulation

Support: NIDA grant DA011064

Title: The novel 5-HT₇ receptor antagonist MC-RG19 attenuates 8-OH-DPAT-induced hypothermia in male and female rats

Authors: ***J. J. HESTERMAN**¹, L. FLORES², B. E. BLASS³, D. J. CANNEY³, R. GAO³, B. A. PAGNI¹

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Abstract: MC-RG19 is a new antagonist that is over 100-fold more selective for serotonin 7 receptors (5HT₇Rs) compared to other serotonin receptor subtypes based on prior binding data. This study is the first to demonstrate the ability of MC-RG19 to act as a 5HT₇R antagonist *in vivo*. We used 8-hydroxy-n,n-dipropylaminotetralin (8-OH-DPAT), which is a 5HT_{1A/7} agonist, to induce hypothermia as previous studies have shown that 5HT₇ antagonists partially reverse the hypothermia produced by 8-OH-DPAT administration. Internal body temperature of adult male and female Sprague-Dawley rats was determined by anal thermometer in 15-minute intervals. Two measurements were taken for baseline, after which animals received 8-OH-DPAT (1 mg/kg, i.p.). After two post-8-OH-DPAT measurements, the rats received MC-RG19 (0, 3, 5.6, or 10 mg/kg, i.p) followed by two additional measurements. Mean temperature change from baseline was analyzed and only subjects that showed at least a 0.5 °C drop in body temperature 30 minutes post-agonist injection during each test were included in the analyses (n=6 for males; n=8 for females). The effect of sex was not significant nor did sex interact with any other variables. Within-subjects ANOVA showed an interaction between MC-RG19 dose and time (p<0.0001) whereby MC-RG19 partially reversed 8-OH-DPAT-induced hypothermia, with a linear increase across doses at the final time point. These data corroborate results of binding experiments designating MC-RG19 as a 5HT₇ antagonist. Thus, MC-RG19 is a useful tool for examining the functional significance of 5-HT₇Rs.

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Poster

071. Thermoregulation: Cool News and Hot Topics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 071.04/TT14

Topic: F.07. Autonomic Regulation

Support: Wallin Neuroscience Discovery Fund, DK102496
DK102496S1
University of Minnesota MnDRIVE

Title: Sympathetic neuromodulation of the brown adipose tissue

Authors: *C. E. LYONS¹, M. RAZZOLI², E. B. LARSON³, D. SVEDBERG⁴, M. SANDERS⁵, M. THOMAS⁷, A. BARTOLOMUCCI⁶

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Abstract: Brown adipose tissue (BAT) is an organ that produces heat from chemical energy and is implicated in adaptive thermogenesis. BAT activation is associated with decreased body fat mass and blood glucose concentrations, making it an intriguing target for anti-obesity therapies. BAT is densely innervated by sympathetic nerves, which are required for tissue development and activation. In this study, we set out to develop novel virally-mediated and genetic models to achieve selective optogenetic activation of the sympathetic nerves innervating the BAT, and establish its effect on BAT thermogenesis. We first developed an AAV6 virus (AAV6-ChR2-eYFP) that retrogradely infects sympathetic nerves, inducing expression of the blue light-sensitive channelrhodopsin-2 (ChR2) and a reporter enhanced yellow fluorescent protein (eYFP). Additionally, we generated a Tyrosine Hydroxylase-Cre X Rosa26-LSL-ChR2-eYFP mouse model (referred to as ChR2TH-Cre⁺ or ChR2TH-Cre⁻). ChR2TH-Cre⁺ mice express Cre recombinase under a tyrosine hydroxylase promoter to drive expression of ChR2 in the sympathetic neurons that innervate the BAT. Using a peripherally implanted optogenetic device, we performed acute optogenetic stimulation of the BAT while BAT and core temperature were simultaneously recorded. Using a 30min light ON protocol we observed rapid and consistent rises in both BAT and core temperature exclusively in ChR2-expressing mice. Virally and genetically-induced expression of ChR2 was confirmed using whole-tissue X-CLARITY and immunohistochemistry to colocalize reporter protein eYFP with tyrosine hydroxylase. Overall, these data validate our novel optogenetic sympathetic neuromodulation approach, and demonstrate that selective activation of the sympathetic nerves is sufficient to elicit acute BAT activation. Further studies will determine the effect of long-term, chronic sympathetic activation of the BAT.

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Poster

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Program #/Poster #: 071.05/TT15

Topic: F.07. Autonomic Regulation

Support: NIH R01-NS091066

Title: Neurons in the ventral lateral preoptic area inhibit brown adipose tissue thermogenesis and muscle shivering

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Abstract: Neurons in the preoptic area of the hypothalamus play important roles in thermoregulation. However, the subregions of the preoptic hypothalamus are heterogeneous. Here we show that in urethane/chloralose-anesthetized, artificially-ventilated rats, nanoinjections of NMDA (0.2mM) targeting the caudal region of the medial preoptic area (MPA), and the ventral part of the lateral preoptic area (vLPO), and the rostral region of the MPA suppressed cold-evoked brown adipose tissue (BAT) sympathetic activity (SNA), and reduced BAT temperature (TBAT) and expired CO₂, and produced a mild hypotension and bradycardia. Inhibition of vLPO neurons (muscimol, 1.2 mM, and AP5/CNQX, 5mM each) increased BAT SNA, and TBAT, accompanied by hypertension and tachycardia. Activation of the MPA inhibits the BAT thermogenesis evoked by AP5/CNQX in vLPO. The inhibition of BAT SNA by vLPO neurons does not require a GABAergic input to DMH, while MPA provides a GABAergic input to DMH. Activation of vLPO neurons inhibits the BAT thermogenesis evoked by NMDA in rRPa, but not after bicuculline in rRPa; which indicates a direct or indirect GABAergic input from vLPO to rRPa. Thermogenesis elicited by vLPO inhibition is dependent on a glutamatergic input to DMH and rRPa, and MnPO is not the glutamatergic source for these thermoregulatory areas. Activation of neurons in the vLPO also inhibits cold- and prostaglandin-evoked muscle shivering, while vLPO inhibition evokes muscle shivering. Thus, vLPO contains neurons tonically active in a warm condition, whose activity is required to maintain the very low levels of BAT thermogenesis and muscle shivering observed when core and skin temperatures are at or greater than the thermoneutral level. The vLPO sympathoinhibitory neurons act through a direct or indirect GABAergic drive to rRPa sympathetic premotor neurons.

Disclosures: E.P. Conceicao: None. C.J. Madden: None. S.F. Morrison: None.

Poster

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Program #/Poster #: 071.06/TT16

Topic: F.10. Food Intake and Energy Balance

Support: JPB Foundation

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Title: Dorsal raphe nucleus gabaergic neurons control adaptive thermogenesis

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Abstract: To maintain energy homeostasis, food intake must be balanced with energy expenditure. Energy expenditure is a combination of three factors: physical activity, basal metabolism, and adaptive thermogenesis. Mammals often live in climates with temperatures above/below body temperature, sometimes far away from average body temperature. Importantly, when exposed to cold or warmth, the mammalian brain triggers an array of autonomic, behavioral, and neuroendocrine responses that defend body temperature against change. Thus, understanding the response to heat/cold and which are the neuronal players involved in this response is essential to understand this process. The key node responsible for thermoregulation is thought to lie in the anterior hypothalamus, particularly the preoptic area (POA) although many other nuclei are capable of regulating thermogenesis to augment or reduce energy expenditure.

In order to identify all the regions in the brain activated by heat/cold we used an unbiased whole-brain activity mapping system (iDISCO+). Notably, areas previously known to be activated in these conditions, such as the POA or the PVH were the top hits. Interestingly, a previously unidentified region activated by heat was amongst the significantly enriched regions, the dorsal raphe nucleus (DRN). Work from our lab previously identified this region as important in regulating feeding; we thus explored a potential role for the DRN in regulating thermogenesis. Here, we show that GABAergic neurons in the dorsolateral portion of the DRN (hereafter, DRN^{Vgat} neurons) are activated by ambient heat and polysynaptically innervate interscapular brown adipose tissue (iBAT). Chemogenetic modulation of these neurons enables bidirectional regulation of energy expenditure through changes in both thermogenesis and locomotor activity. Finally, using whole-mount projection mapping and projection-specific optogenetic manipulations, we find that DRN^{Vgat} neurons project broadly throughout the brain and are capable of regulating iBAT thermogenesis through downstream circuits in the hypothalamus and extended amygdala. Together, our work establishes the DRN as a key nucleus in the control of energy balance.

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Poster

071. Thermoregulation: Cool News and Hot Topics

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Program #/Poster #: 071.07/TT17

Topic: F.10. Food Intake and Energy Balance

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Title: PVH^{BDNF} neurons regulate browning of inguinal white adipose tissue (iWAT)

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Abstract: Obesity results from a chronic positive balance. To find therapeutic targets for obesity, we attempt to elucidate neural circuits that govern energy expenditure. Energy-storing white adipose tissue (WAT) and energy-utilizing brown adipose tissue (BAT) are potential therapeutic targets for treatment. Under certain physiological conditions, such as cold exposure or β adrenergic stimulation, white adipocytes can transdifferentiate into brown adipocyte-like cells (termed "browning"). We recently found that BDNF expressed in the paraventricular hypothalamus (PVH) is essential for thermogenesis in the interscapular BAT (iBAT) leading to energy expenditure. However, it is unclear if PVH^{BDNF} neurons also contribute to thermogenesis in inguinal WAT (iWAT).

We used transneuronal retrograde tracing in *Bdnf*^{lacZ/+} reporter mice in order to determine if distinct PVH^{BDNF} neurons are connected to iBAT and iWAT. We simultaneously injected retrograde pseudorabies virus PRV-152 into iWAT and PRV-614 into the iBAT of *Bdnf*^{lacZ/+} mice. Upon examination PRV-152 and PRV-614 expression in PVH^{BDNF} neurons, we found that the majority of iWAT and iBAT projecting neurons in the PVH do not overlap although there is a sparse population of neurons that do overlap. In accordance with previous studies, most iBAT and iWAT projecting PVH^{BDNF} neurons also show spatially distinct innervation of the spinal cord. More specifically, iBAT projecting PVH^{BDNF} neurons populated the upper portion of the spinal cord whereas iWAT projecting PVH^{BDNF} neurons populated the lower portion. Taken together, these observations suggest that PVH^{BDNF} neurons that connect to iWAT are distinct from the PVH^{BDNF} neurons that connect to iBAT. To determine the role of PVH^{BDNF} neurons in browning of iWAT, I utilized Cre-dependent viruses to activate or inhibit BDNF in the PVH. To selectively activate PVH^{BDNF} neurons, I bi-laterally injected a Cre-dependent adeno-associated virus (AAV) that expresses the excitatory designer receptor exclusively activated by designer drug (DREADD) hM3Dq (pAAV-hSyn-DIO-hM3D(Gq)mCherry) into the PVH of *Bdnf*^{Cre/+} mice. These mice were then treated mice with clozapine-n-oxide (CNO) to stimulate these

neurons. To selectively delete BDNF in the PVH, I injected AAV-Cre-GFP bi-laterally into the PVH of *Bdnf^{lox/lox}* mice. These mice were then subjected to 4°C for 2 weeks. We will report the effects of activation/deletion of BDNF in the PVH on iWAT browning by examination of core-body temperature, gene and protein expression of thermogenic markers, and histology of iWAT sections.

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Poster

071. Thermoregulation: Cool News and Hot Topics

Location: SDCC Halls B-H

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Program #/Poster #: 071.08/TT18

Topic: F.03. Neuroendocrine Processes

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Title: Immunohistochemical and morphometric differences between DRG and nodose sensory neurons innervating the pancreatic islets of the rat

Authors: M. E. PEARCE¹, T. L. REDLER¹, H. D. NGUYEN¹, V. P. DUGAN¹, M. L. CAMPBELL-THOMPSON², *R. D. JOHNSON¹

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Abstract: Current treatments for diabetes mellitus are not fully effective and can lead to decreased quality of life and potentially lifelong complications. Neuromodulation therapies (stimulation/blocking) directed towards pancreatic nerve subpopulations might decrease pancreatic inflammatory responses and increase revascularization of islets to support beta-cell function. To provide a more detailed neuroanatomical map of the pancreatic sensory supply, the present study characterized dorsal root ganglion (DRG) and nodose ganglion (NG) neurons innervating the rat pancreas to determine their immunohistochemical and morphometric phenotype. Aseptic surgical exposure of the pancreas in anesthetized mature male Sprague-Dawley rats was followed by several 1µL injections of a retrograde fluorescent tracer, DiI paste, delivered through a pulled/beveled glass micropipette via pressure injector pulses. After 13-20d recovery, the animals were euthanized and transcardially perfused with phosphate buffered saline (PBS, pH 7.4) followed by 4% paraformaldehyde in PBS. Bilateral T8 and T11 DRGs and nodose ganglia were dissected free, post-fixed overnight and cryoprotected in 30% sucrose solution. Serial ganglion cryosections at 14µm were thaw-mounted onto two alternating slides. Pancreatic cryosections (30-50µm) were obtained for confocal imaging. DiI-positive cells/axons were visualized via standard multi-label IHC fluorescence microscopy with Zeiss optics and the

images digitized. Labeling for CGRP and TRPV-1 was found bilaterally in most DiI-positive DRG cells from the pancreas, with TRPV-1 and CGRP positively co-labeling in cells 93.0% of the time whereas only 45.1% of the CGRP positive cells co-localized Substance P. Cells positively co-labeled with CGRP and Neurofilament-M (NFM) 44.2% of the time and exhibited a significantly larger diameter ($40.6 \pm 0.9\mu\text{m}$) compared to CGRP positive/NFM negative neurons ($36.3 \pm 1.2\mu\text{m}$). Confocal images of the islets showed peptidergic afferent axons running with the vasculature but not co-localizing with sympathetic axonal marker tyrosine hydroxylase. Bilaterally, the pancreatic NG neurons were mostly negative for NFM and neuropeptides and exhibited significantly smaller diameters compared to pancreatic DRG neurons. Almost all pancreatic DRG neurons, but not NG neurons, exhibit an IHC marker phenotype consistent with likely roles in nociception, vascular control, and inflammatory signaling, via sensory and paracrine mechanisms. In contrast to DRG neurons, vagal (NG) pancreatic sensory neurons (i) do not likely innervate the vasculature and (ii) have predominantly unmyelinated fibers.

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Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.01/TT19

Topic: G.02. Motivation

Title: Effects of dopaminergic compounds on motivation in a marmoset novel effort discounting task

Authors: *T. ENOMOTO¹, N. KONOIKE², A. TAKEMOTO², K. NAKAMURA², K. IKEDA¹
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Abstract: Motivational deficits are common symptoms in a wide range of neuropsychiatric disorders. Effort-based decision making paradigms have recently been used for measuring motivation in humans. Since the prefrontal cortex is a critical component in effort-based decision making, the non-human primates which have the well-developed prefrontal cortex would be useful in the translational research for motivational deficits. In the present study, we developed a novel effort discounting paradigm using a touch-panel system in common marmosets. Five to seven adult common marmosets per group were used, and the effects of pharmacological manipulation were assessed in a cross-over design. Marmosets were tested to choose between low-reward (a piece of cake) requiring low-effort (a touch-response) versus high-reward (three pieces of cake) requiring one of three different efforts (one, two or four touch-responses). Since number of trials per session kept constant, choosing the high-reward option was always the

optimal strategy to obtain the maximum numbers of reward. When effort requirement was changed in either ascending or descending ratio, marmosets' high-reward choice was reduced as physical effort requirement was increased. It suggests that marmosets could make decision on the basis of cost/benefit evaluation. Dopamine D₁ receptor antagonist SCH-39166 (0.03 mg/kg i.m.) did reduce the marmosets' high-reward choice, only when larger effort was required to receive high-reward than low-reward. These results suggest that the blockade of dopamine D₁ receptors could reduce the motivation to exert the physical effort to obtain higher reward, and it would not be attributable to the alternation in reward preference, cognitive and motor functions. On the other hand, dopamine D₂ receptor antagonist raclopride (0.01-0.03 mg/kg i.m.) unexpectedly failed to affect high-reward choice, although it did increase the omission which might be related with the deficits in activating aspect of motivation. This behavioral paradigm would be useful in the translational research for motivational deficits.

Disclosures: **T. Enomoto:** A. Employment/Salary (full or part-time); Sumitomo Dainippon Pharma Co., Ltd.. **N. Konoike:** None. **A. Takemoto:** None. **K. Nakamura:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant from Sumitomo Dainippon Pharma, Co., Ltd. **K. Ikeda:** A. Employment/Salary (full or part-time); Sumitomo Dainippon Pharma Co., Ltd..

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

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Program #/Poster #: 072.02/TT20

Topic: G.02. Motivation

Support: NEI Intramural

Title: Specialized populations of dopamine neurons in monkey substantia nigra

Authors: ***M. G. COSTELLO**, D. B. T. MCMAHON, O. HIKOSAKA
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Abstract: Rewards and punishments are opposites in terms of their practical meaning, yet both are salient events that provoke arousal and attention. Whereas dopamine (DA) neurons in the substantial nigra pars compact (SNc) have long been known to convey reward prediction error signals appropriate for reinforcement learning, previous work from our lab showed that SNc contains a separate class of neurons that signal salience by responding comparably to reward vs. punishment predicting stimuli (Matsumoto and Hikosaka 2009). More recent work from the lab showed that SNc also contains DA neurons corresponding to an altogether different functional

dichotomy, termed sustain-type and update-type DA neurons (Kim et al 2015). Sustain-type neurons encode the long-term stable values of visual objects even when reward is not expected, whereas update-type DA neurons cease responding to previously trained good stimuli in unrewarded contexts. Importantly, in both studies the two classes of DA neurons discovered were found in anatomically separate regions of SNc: both salience- and sustain-type cells were common in the dorsal-lateral region (dlSNc), while value and update cells were found in the ventral-medial region (in vmSNc). This anatomical pattern raises the possibility that salience- and sustain-type neurons in dlSNc are one in the same, and likewise value- and update-type neurons in vmSNc. Here we tested this hypothesis by recording from neurons throughout SNc using a battery of tasks chosen to assay both the salience/value and sustain/update dimensions of DA neuron properties. In recordings to date from one monkey, DA single neurons were screened in a Pavlovian task that contrasted responses to conditioned stimuli associated with reward or punishment. We tested the same cells with other assays of learned-value association, including passive viewing, object-value, and reversal tasks, and otherwise assessed neurons for sustain- vs. update-type properties. As expected, some DA neurons in dlSNc showed both salience- and sustain-type responses, while other DA neurons in vmSNc showed both value- and update-type responses. However, we also found some DA neurons that showed both salience- and update-type responses. These findings raise the possibility that there are several groups of DA neurons whose visual responses are modulated by multiple dimensions of context.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.03/TT21

Topic: G.02. Motivation

Support: NIH Grant P01 NS044393

Title: Reward-dependent modulations of local field potentials reflect dopaminergic and non-dopaminergic activities within the primate midbrain

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Abstract: Midbrain dopamine neurons are thought to play a crucial role in motivating behaviors toward desired goals. While it is well established that the single-unit spiking of dopamine neurons adheres closely to the reward prediction error signal predicted by models of reinforcement learning, much less is known about the dynamic coordination of population-level

neuronal activities in the midbrain. Here we used local field potentials (LFPs) recorded from the substantia nigra pars compacta (SNc) of behaving monkeys to investigate how those population-level signals are modulated during an operant task and related to the spiking activity of dopamine neurons. We found that discrete frequency bands in the LFP were modulated transiently by reward-related events, predicting and responding to reward delivery, while disregarding processes related to movement execution. For low-frequency components of the LFP (5-32-Hz) we found that power correlated positively with the size of rewards predicted by an instruction cue and phase was locked to the spiking of dopamine neurons. For high frequency components (33-120-Hz), in contrast, power was anti-correlated with reward value during a post-instruction delay period and phase held no consistent relation to dopamine spiking. Around the time of reward delivery, LFP (mainly beta band) encoded the actual quantity of reward received rather than reward prediction error. These results suggest that LFPs recorded from the vicinity of the SNc reflect the activity of inputs to midbrain dopamine neurons. In other brain regions, inhibitory interneurons often play a central role in the generation of gamma-band LFP. Thus, it is intriguing that gamma-band LFP power was anti-correlated with reward value. Together, LFPs provide insights into the distinct processing of reward information subserved by dopaminergic and non-dopaminergic components of the midbrain.

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Poster

072. Dopaminergic Reward Systems

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.04/TT22

Topic: G.02. Motivation

Support: JSPS KAKENHI 18K03194

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Title: Social reward signals in the medial prefrontal cortex and the lateral hypothalamus of the macaque

Authors: ***A. NORITAKE**¹, T. NINOMIYA¹, M. ISODA²

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Abstract: Valuation of rewards to oneself is influenced by rewards to others. Such subjective reward valuation profoundly shapes behavior in social life. Previous studies have revealed that the medial prefrontal cortex (MPFC) and the lateral hypothalamus (LH) are involved in processing reward to oneself and others. However, it remains unclear whether and if so how

these structures interact each other to evaluate rewards in social contexts. To address this issue, we devised a social Pavlovian conditioning procedure using two monkeys (M1 and M2). In the procedure, they faced each other across a visual display screen. A visual conditioned stimulus shown at the screen differently signaled each monkey's reward probability and a liquid reward was delivered to either M1, M2, or no one. The animals were exposed to two alternating reward contexts: a self-variable block and a partner-variable block. In the self-variable block, the probability of M1's reward varied ($P = 0.25 - 0.75$), whereas the probability of M2's reward was constant ($P = 0.2$). In the partner-variable block, the probability of M2's reward was variable ($P = 0.25 - 0.75$), whereas the probability of M1's reward was constant ($P = 0.2$). Using this procedure, we previously showed that the monkeys lower their own reward value as their partner's reward probability increases (364.09, SfN2014). We also showed that neurons in the MPFC and the LH encode information about self-rewards and partner's rewards (364.10, SfN2014; 67.16, SfN2016). To clarify functional connectivity between these brain regions, local field potentials (LFPs) were recorded simultaneously in the MPFC and the LH using multi-contact electrodes during the conditioning procedure. We found that following the stimulus presentation, coherences increased between the two regions and phase modulation in the MPFC occurred significantly earlier than that in the LH. Moreover, intensity of phase-amplitude coupling (PAC) between the phase signals in the MPFC and the amplitude signals in the LH better correlated with the partner-reward probability than with the self-reward probability. Correlations between the PAC intensity and the self/partner-reward probability were less prominent in the coupling between the phase signals in the LH and the amplitude signals in the MPFC. These findings indicate that the functional connectivity between the cortico-subcortical regions dynamically changes during social reward evaluation. We suggest that the MPFC provides the LH with modulatory top-down signals for processing information about others' reward.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.05/TT23

Topic: G.02. Motivation

Support: NIH 1U01NS094375-02

Title: Chronic intranasal oxytocin modulation of dopamine release in the nucleus accumbens is sub-region specific

Authors: ***P. POPOV**¹, **P. R. PATEL**², **C. M. CALDWELL**², **D. CAI**³, **J. D. BERKE**⁴, **C. A. CHESTEK**², **J. B. BECKER**¹

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Abstract: Mesolimbic dopamine (DA) neurons in the ventral tegmental area (VTA) play an important role in motivation, reward processing and drug addiction. Separate populations of DA neurons project to distinct sub-regions within the ventral striatum, the principal afferent of mesolimbic DA neurons, and mediate unique aspects of reward-motivated behavior. We know that the Nucleus Accumbens Core (NAcC) is responsible for acquisition of a cue reward association, coding the value of work and relapse of drug use. The Nucleus Accumbens Shell (NAcS), on the other hand, is important in formation of a pair bond, incentive salience and valence properties of a cue. Yet, we have much to learn about the dynamics of DA release across these sub-regions. Fast-scan cyclic voltammetry (FSCV) is a technique of choice for questions that involve in vivo neuromodulator signaling due to its sub-second temporal resolution and high sensitivity. However, current FSCV electrodes are limited to a single region of interest and are often plagued with inconsistent long-term performance. As part of the Brain Initiative collaboration, our group developed a 16-channel multi-array electrode capable of monitoring dopamine release simultaneously across multiple brain locations. With this novel tool we investigated changes in DA release in NAcC and NAcS for over 60 days in the same animal for the first time. We were also able to examine variations between distinct local microenvironments within brain regions. Furthermore, stable long-term recording allowed us to observe how chronic treatment with oxytocin, a potent mediator of protective effects of a social environment on drug taking behavior, modulates electrically evoked DA signaling within the NAcC and NAcS in both male and female rats after treatment with a psychomotor stimulant. We find differential effects of oxytocin on DA release in NAcC and NAcS.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.06/TT24

Topic: G.02. Motivation

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Title: Effect of oxytocin receptor activation in nigro-striatal pathways impulsive choice and striatal dopamine release

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Abstract: A key measure of impulsive choice involves assessment of preference for smaller reinforcement but delivered immediately versus larger rewards associated with delay. This type of behavior has been used as a predictor of several neuropsychiatric disorders, including: personality disorders, attention deficit hyperactivity disorder (ADHD) and addiction. All these pathologies, are linked to a dysfunction in dopaminergic transmission. It has been described that changes in cortico-striatal connections by bottom-up regulation are closely related to this type of behavior, and that changes in patterns of functionality linked to a decreased in dopaminergic system activity, contribute to the induction of high levels of impulsive choice. In addition, the findings of more recent research suggest that oxytocin (OXT) may modulate several behaviors linked to the dopaminergic system and that bidirectional modulation between these systems may occur. There is evidence that, oxytocinergic system can activate mesocorticolimbic pathway, for example, it has been suggested that OXT perfusion in the midbrain dopamine cell body regions induces an increase in extracellular dopamine (DA) levels in striatal nuclei. On the other hand, it has been shown that an increase in the dopaminergic activity in amygdala induces a rise in OXT extracellular levels. Notably, these systems also mediate impulsive choice. Given these findings, our objective was to study the role of oxytocinergic system in the modulation of nigro-striatal dopaminergic transmission and its modulation of impulsive choice. Adult male Long-Evans rats were well-trained on a delay discounting task, where they chose between a smaller (1 pellet) reward delivered immediately, or a larger 4-pellet reward delivered after a delay (0-45 s). On separate test days, they received infusions of the OXT-R agonist (WAY267464 dihydrochloride, at a dose of 3g/0.5l) in the substantia nigra pars compacta (SNpc). These treatments decreased impulsive choice, in that rats displayed a greater preference for larger, delayed rewards. Complementary studies using in vivo microdialysis in adult male Sprague Dawley rats revealed that perfusion of same agonist in SNpc, induces an increase in extracellular DA level in dorsolateral striatum (DLS). These results encourage further investigation of the neurobiological mechanisms that underlie the type of modulation exerted by oxytocinergic system and its possible modulatory role in impulsive choice behavior associated with pathologies that present a dysfunction of the dopaminergic and oxytocinergic system in the nigro-striatal pathway.

Disclosures: M. Moreno: None. J. Fuentealba: None. S. Floresco: None. M. van Holstein: None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.07/UU1

Topic: G.02. Motivation

Support: NIH Grant DA042362

Title: Dopamine's role in changing subjective preference

Authors: *M. J. LEFNER, A. P. MAGNON, M. R. LOPEZ, J. GUTIERREZ, M. J. WANAT
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Abstract: Decision-making policies are often influenced by sunk costs, or rather retrospective costs that cannot be recovered. For example, enduring a longer wait (temporal cost) before a reward is delivered can increase the perceived value of the reward. However, it is not known if incurred temporal costs can subsequently alter the relative preference between rewards. Given that reward-evoked dopamine release scales with increasing temporal costs, we hypothesized that dopamine release in the ventromedial striatum mediates changes in subjective preference between different flavored food rewards.

To address this question we developed a training paradigm in which we could alter the relative preference between banana and chocolate flavored food pellets by manipulating the inter-trial interval before the food reward was delivered. The relative motivation to work for the different flavored food rewards was then assessed in a progressive ratio task in which the operant requirement scales independently for the distinct rewards. Surprisingly, our data indicates dopamine is not required for acquiring the change in subjective preference. However, preliminary data suggests dopamine may be critical for the expression of changes in subjective preference as evidenced by voltammetry recordings of dopamine release in the ventral striatum and optogenetic manipulations of midbrain dopamine neurons. These findings highlight the involvement of the mesolimbic dopamine system in the expression of changes in subjective preference evoked by manipulating incurred temporal costs.

Disclosures: M.J. Lefner: None. A.P. Magnon: None. M.R. Lopez: None. J. Gutierrez: None. M.J. Wanat: None.

Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.08/UU2

Topic: G.02. Motivation

Support: KAKEN 15K01837
KAKEN 16K16648
KAKEN 16H05135
KAKEN 15K11328

KAKEN 26460328

Title: Is it possible that non-attractive male mouse can get attractive mind set?

Authors: *Y. N. OHNISHI¹, Y. KAWAHARA², Y. H. OHNISHI², A. NISHI²
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Abstract: To attract female is an eternal theme for male. Last year, we reported attractiveness of male mice was based on their appearance, and microdialysis analyses of female nucleus accumbens revealed that mesolimbic dopamine system is activated against attractive male mouse at the second encountering, but not against non-attractive male mouse. So, we examined whether optogenetic stimulation of the female mesolimbic dopamine pathway at the time to be close to non-attractive male mouse increases the residence time in the interaction area of non-attractive male mouse in the male preference test. However, the results showed the optogenetic stimulation of the female mesolimbic pathway had restricted effects on attractiveness of non-attractive male mouse. Next, we found different factors except male appearance about male attractiveness. We call it “attractive mind set” of male mice in this point. For example, non-attractive experience of attractive male mouse decreased the interaction time as attractive index in the male preference test. In other words, male mental condition could make effects on his attractiveness. We have reported social defeat paradigm in mice made similar mental condition to depression, and the defeated male mice showed anhedonia phenotype in the sucrose preference test. We found similar results in the male female preference test. In the experiments, the defeated male mice didn't show female preference like as normal or resilient mice. Now, we are trying to examine how the attractive mind set of male mice increases or decreases male attractiveness in several conditions including social defeat paradigm.

Disclosures: Y.N. Ohnishi: None. Y. Kawahara: None. Y.H. Ohnishi: None. A. Nishi: None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

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Program #/Poster #: 072.09/UU3

Topic: G.02. Motivation

Support: CIHR FDN-148473

Title: Sexually dimorphic endocannabinoid-mediated plasticity in the VTA after acute fasting

Authors: *N. J. GODFREY¹, M. QIAO², S. L. BORGLAND²
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Abstract: Dopamine neurons in the ventral tegmental area (VTA) are important for energizing goal directed behaviour towards food. These neurons are sensitive to changes in metabolic states as they respond to peripheral peptides that signal hunger, satiety or stress. Acute fasting increases the incentive motivation for food as well as the mobilization of energy stores by increasing corticosterone. We tested if there were sexually dimorphic effects on dopaminergic synaptic transmission in the VTA after acute (16h) fasting. We found no changes in amplitude or frequency of mIPSCs or mEPSCs or changes to the AMPAR/NMDAR ratio following fasting. However, we found endocannabinoid-mediated depolarization-induced suppression of inhibition (DSI) was significantly greater in females than male control mice. Further, DSI was significantly diminished in female but not male fasted mice. In contrast, depolarization-induced-suppression of excitation (DSE) was enhanced in female but not male fasted mice. In attempt to determine the VTA input that is responsible for this change, we selectively photostimulated fibers in the VTA projecting from excitatory cells of the Lateral Hypothalamus (LH). We show here that, although the LH projection is sensitive to endocannabinoids, the changes that occur following fasting are not observed in this projection. Taken together, these results demonstrate that fasting suppresses excitatory inputs, while facilitating inhibitory inputs, to the VTA in females but not males; indicating that the mesolimbic circuit of males and females respond differently to energy deprivation.

Disclosures: **N.J. Godfrey:** None. **M. Qiao:** A. Employment/Salary (full or part-time);; University of Calgary. **S.L. Borgland:** None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.10/UU4

Topic: G.02. Motivation

Title: Rapid dopamine release in male mice accompanies exposure to female odorant cues

Authors: ***I. GILDISH**, D. P. COVEY, A. C. PUCHE, M. T. SHIPLEY, J. F. CHEER
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Abstract: Reproductive physiology and sexual behavior are primarily regulated by chemical compounds emitted by a conspecific of the opposite sex. These chemosensory cues are initially detected and processed by the olfactory system and are theorized to facilitate sexual behavior through a neural network that integrates several exteroceptive stimuli such as social and hormonal cues. Once this sensory information reaches brain regions that are involved in sexual behavior it promotes social engagement. One of these areas is the nucleus accumbens, an important node of motivational networks, which receives dense dopaminergic afferentation from the ventral midbrain. Here, we utilized fast-scan cyclic voltammetry in behaving male mice, to

assess whether olfactory cues originating from females at different stages of the estrous cycle engage subsecond dopamine release in a cycle-specific fashion. We further tested the dopaminergic response of male mice to female odorant cues in the absence of the female conspecific. We record robust dopamine release that depends on the phase of the estrous cycle and report that dopamine is preferentially engaged when male mice are exposed to the female conspecific compared to presentation of a vaginal swab. Because subsecond dopamine release events, such as the ones observed in our experiment, are tightly controlled by endocannabinoids we are testing the role of signaling at CB1 receptors in these motivational responses and hypothesize that the dopaminergic effects of odorant cues in the nucleus accumbens will be potentiated by pharmacological elevation of endocannabinoid levels in a CB1 receptor-dependent fashion.

Disclosures: **I. Gildish:** None. **D.P. Covey:** None. **A.C. Puche:** None. **M.T. Shipley:** None. **J.F. Cheer:** None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

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Program #/Poster #: 072.11/UU5

Topic: G.02. Motivation

Support: National Institute of Mental Health: MH048404
Conacyt, Mexico. Estancia postdoctoral. CVU:332983

Title: Sex differences in the dynamics of dopamine release and neuronal activity

Authors: ***M. RIVERA-GARCÍA**, T. G. CHOWDHURY, B. MOGHADDAM
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Abstract: Clinical and preclinical studies have suggested sex differences in dopaminergic system dynamics. For example, neurochemical and behavioral effects in response to psychoactive drug administration and performance in dopamine-dependent cognitive tasks are different between males and females. Although structural sex differences in the mesocorticolimbic circuit have also been described, less is known about sex differences in dopaminergic neuron activity and its effect on dopamine efflux. Here, we have attempted to characterize sex differences in dopamine neuron activity and dopamine release in the dorsal striatum (DS) and nucleus accumbens (NAc). We have performed awake-behaving electrophysiological recordings from ventral tegmental area (VTA) in male and female rats during acquisition of a fixed ratio 1 (FR1) appetitive operant conditioning task followed by extinction. In addition, we have measured extracellular dopamine levels in the DS and NAc of freely moving rats in response to two electrical stimulation protocols in the VTA as we measured

their motor behavior. Our results show that fast-burst stimulation of VTA induces a greater increase in dopamine levels in the NAc of males compared to females, whereas the sustained phasic stimulation pattern produces a larger dopamine release in females. On the other hand, in the DS, both stimulation protocols increase dopamine levels similarly in males and females. The electrophysiological data on basal firing rate and phasic responses to cue and reward during leaning and extinction are being analyzed. These data may have implications for sex differences in dopamine-related affective functions and related disorders.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.12/UU6

Topic: E.03. Basal Ganglia

DA034140

AA020098

Title: Gender differences in voluntary wheel running during adulthood is associated with distinct adaptations in the dopaminergic system in the dorsal striatum

Authors: A. MANDYAM¹, M. PAVLICH², M. TERRANOVA², *C. D. MANDYAM³
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Abstract: The central function of the dopaminergic system is to control motivation for natural rewards and motor movement, and several studies in rodents suggest certain aspects of dopaminergic functioning may contribute to the genetic/biological regulation of voluntary wheel running. Adult female rats show greater running output compared with age-matched male rats, however, it is not known whether gender differences in midbrain dopaminergic system may account for behavioral differences in running output. Next, it is unknown if the lower running output in adult male rats can be regulated by wheel running experience during adolescence, and whether experience to wheel running during adolescence will diminish the gender differences in running output during adulthood. We therefore determined the exercise output in adult male rats that either had initiated voluntary wheel running only during adulthood or during adolescence and compared them with adult female rats that had initiated voluntary wheel running only during adulthood. We also determined the alterations in the expression of tyrosine hydroxylase in the dorsal striatum and the number of tyrosine hydroxylase expressing neurons in the substantia nigra to evaluate the association between levels of tyrosine hydroxylase and running output. Our results demonstrate that exercise output in adult male rats were significantly higher when

running was initiated during adolescence, and this higher exercise output was not significantly different from running output in adult female rats. Expression and number of tyrosine hydroxylase neurons in the dorsal striatum and substantia nigra were significantly higher in adult female nonrunners compared with adult male nonrunners and running reduced the expression and number of tyrosine hydroxylase neurons in adult female rats without producing any significant changes in adult male rats. Our results directly demonstrate that the higher running output in adult female rats was predicted by lower amounts of tyrosine hydroxylase in the dorsal striatum and lower number of tyrosine hydroxylase expressing neurons in the substantia nigra and this effect of wheel running on dopaminergic activity was gender specific. Our results suggest that the amount of dopamine production and turnover is lower in adult female rats that had escalated running activity, and this effect may be important for overall gender differences in exercise output levels.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.13/UU7

Topic: G.02. Motivation

Support: NIH Grant R01DA039952 to JBB

Title: G-protein coupled estradiol receptor 1 activation regulates drug preference and dopamine release in male rats

Authors: *J. A. QUIGLEY, J. B. BECKER
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Abstract: There are sex differences in motivation for cocaine and cocaine-taking behavior in rodents. Susceptibility to addiction and addiction-like behaviors in females are modulated by estradiol. Research from the Becker laboratory has shown that estradiol enhances the cocaine-induced increase in dopamine in the dorsal striatum of female rats, but not male rats. This enhanced increase in dorsal striatum dopamine is thought to mediate the increased susceptibility of females to addiction and drug abuse. The role of estradiol, and other gonadal hormones, on addiction-like behaviors in males, however, is not well understood. Research from the Becker laboratory finds that estradiol does not enhance cocaine taking behavior of castrated male rats. In these experiments, intact male rats were tested on a conditioned place preference (CPP) paradigm with cocaine (10 mg/kg i.p.). The estradiol receptor antagonist, ICI182,780 (ICI) was dissolved in ethanol with cholesterol (1:10), evaporated to dryness and then administered via

intracranial cannula in dorsal striatum. ICI reduced the time spent in the drug-paired chamber on test day, compared to cholesterol-treated males. There are three identified estradiol receptors: estradiol receptor (ER) α , ER β and g-protein coupled estradiol receptor 1 (GPER-1). While ICI is an antagonist at ER α and ER β , it is an agonist at GPER-1. We then investigated the effects of activation of GPER-1 on CPP in intact male rats. The GPER-1 agonist, G1 was dissolved with cholesterol (G1:cholesterol; 1:10) or cholesterol alone as above and delivered to dorsal striatum. Results indicate that G1 treatment reduced the time spent in the drug-paired chamber on test day, compared to cholesterol treated males. These data indicate that while estradiol enhances drug-taking in females, in males it reduces preference for drug via GPER-1. We hypothesize that GPER-1 activation is attenuating DA release in response to cocaine in males. Current experiments are utilizing *in vivo* microdialysis to investigate this. These findings further our understanding of how GPER-1 may play a crucial role in sex differences in the formation of drug preference and addiction.

Disclosures: J.A. Quigley: None. J.B. Becker: None.

Poster

072. Dopaminergic Reward Systems

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Topic: G.02. Motivation

Support: NIDA DA039952

Title: Estradiol-induced potentiation of dopamine release in dorsal striatum following amphetamine administration requires estradiol receptors and mGluR5

Authors: *Z. SONG¹, H. YANG³, E. M. PECKHAM⁴, J. B. BECKER^{1,2}

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³Brain Res. Inst., UCLA, Los Angeles, CA; ⁴Concordia Univ., Ann Arbor, MI

Abstract: Estradiol potentiates behavioral sensitization to cocaine as well as self-administration of cocaine and other drugs of abuse in female rodents. Furthermore, stimulated dopamine (DA) in dialysate from the dorsolateral striatum (DLS) is rapidly enhanced by estradiol, and it is hypothesized that this enhanced DA release mediates the more rapid escalation of drug taking seen in females, compared with males. The mechanisms mediating the effect of estradiol to enhance stimulated DA release was investigated in this study. Using *in vivo* microdialysis and high performance liquid chromatography (HPLC) coupled with electrochemical detection (ECD), we first examined the effect of estradiol administered through reverse dialysis on amphetamine-induced increase in DA in the DLS of ovariectomized female rats. We then tested if the potentiation of this DA increase could be blocked by the estradiol receptor antagonist, ICI

182,780, or an antagonist to the metabotropic glutamate receptor subtype 5 (mGluR5), 2-Methyl-6-(phenylethynyl)pyridine (MPEP). There is evidence that estradiol receptors collaborate with mGluR5 within caveoli in DLS and mGluR5 are hypothesized to mediate many of the effects of estradiol in the addiction processes in females. Our data show that intrastriatal estradiol significantly enhances the DA response to amphetamine (2.5 mg/kg, i.p.). Either ICI 182,780 infused by reverse dialysis into the DLS or MPEP ip injections prevented the effect of systemic estradiol (5 µg estradiol benzoate, s.c.) to enhance DA release 30 min later. Importantly, our results also showed neither ICI 182,780 or MPEP alone is able to influence the DA response to amphetamine when estradiol is not administered, suggesting that ICI 182,780 and MPEP act via estradiol receptors. Taken together, our findings demonstrate that estradiol potentiates amphetamine-stimulated DA release in the DLS and this effect requires both estradiol receptors and mGluR5 in the DLS.

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Poster

072. Dopaminergic Reward Systems

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Topic: G.02. Motivation

Support: NIH Grant DA019670
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NIH Grant AG042596
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NIH Grant DA036979

Title: Lack of sex differences in d-amphetamine-induced dopamine release measured with Fallypride PET

Authors: *C. T. SMITH¹, L. C. DANG¹, D. T. SAN JUAN¹, S. F. PERKINS¹, L. L. BURGESS¹, D. K. SMITH¹, R. L. COWAN², N. T. LE³, R. M. KESSLER⁴, G. R. SAMANEZ-LARKING⁵, D. H. ZALD¹

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Abstract: Sex differences in the dopaminergic response to psychostimulants could have implications for drug abuse risk and other psychopathology involving dopamine (DA), but human data are limited and mixed. Here, we investigated sex differences in DA release after oral

d-amphetamine (dAMPH) administration using ^{18}F -Fallypride Positron Emission Tomography (PET) in two independent datasets. Dataset 1 consisted of previously published DA release data in young adults (aged 19-29) and contained 18 females (age=22.9±3.0), 16 males (age=21.8±3.2). Dataset 1 scan order was fixed as 1) Placebo, 2) dAMPH, with participants blind to drug administration order. Dataset 2 consists of data from a current study in participants aged 20-30 (young adults, YA) and 50-65 (older adults, OA). Our analyzed data consisted of 21 females (10 YA, 11 OA; age=40.2±3.3), 16 males (10 YA, 6 OA; age=37.3±3.5). Dataset 2 drug order was randomized with participants blind to administration on each visit; ~50% received dAMPH first. All female participants were either postmenopausal (n=10), on hormonal birth control (n=18), or naturally cycling (n=11), in which case they completed both PET scans within the first 10 days of their menstrual cycle. dAMPH (0.43 mg/kg) or placebo was administered orally 3 hours prior to the PET scan. Serial scan acquisition started simultaneously with a 5.0 mCi slow bolus injection of DA D2/3 tracer ^{18}F -Fallypride with the total scan time including two breaks and CT attenuation scans lasting ~3.5 hours. Fallypride binding potential (BP_{ND} , a ratio of specifically bound Fallypride to its non-displaceable concentration) was estimated voxelwise using a simplified reference tissue model in PMOD software (reference region=cerebellum). The resulting BP_{ND} maps for placebo and dAMPH days were linearly registered to one another and the difference in BP_{ND} maps after dAMPH was calculated as $\% \Delta \text{BP}_{\text{ND}}$, with an increase in $\% \Delta \text{BP}_{\text{ND}}$ corresponding to an increase in synaptic DA release. Using both *a priori* anatomical regions of interest based on previously reported sex differences in $\% \Delta \text{BP}_{\text{ND}}$ as well as voxelwise analyses, we failed to detect significant sex differences in $\% \Delta \text{BP}_{\text{ND}}$ in either Dataset. Furthermore, plasma estradiol did not correlate with $\% \Delta \text{BP}_{\text{ND}}$ and this measure did not differ in females on and off hormonal birth control. Our data do not support the presence of observable sex differences in d-amphetamine induced DA release, despite the number of females studied in each dataset here being larger than in any published study of sex differences in $\% \Delta \text{BP}_{\text{ND}}$. As such, sex differences in addiction vulnerability are most likely related to other aspects of the DA system or nondopaminergic mechanisms.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.16/UU10

Topic: G.02. Motivation

Support: MH108837
MH078064

Title: VTA-DH circuits mediate morphine addiction and chronic pain

Authors: Y. HAN¹, M. V. CENTENO², A. L. GUEDEA¹, C. GAO³, A. V. APKARIAN², *J. M. RADULOVIC¹

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Abstract: The long-term prescription of opioids to patients suffering from chronic pain has proved to be of limited success in alleviating pain, while creating an epidemic of addiction and associated deaths. Memories of contexts associated with use of opioid often retain their rewarding features even after prolonged abstinence, and are thus viewed as important causes of long-term opioid craving. The dorsal hippocampus (DH) plays a central role in the processing of context memory, and may therefore contribute to addiction-related behaviors in drug-associated contexts. Furthermore, the DH undergoes significant molecular, cellular, and structural changes during the transition to chronic pain, some of which causally contribute to the persistence of chronic pain. Accumulating evidence suggests that the mesolimbic ventral tegmental area (VTA) plays an important role in mediating chronic pain and addiction. We therefore set out to determine the role of VTA projections to DH in drug-seeking behavior and chronic pain. Using spared nerve injury (SNI) to model chronic pain and conditioned place preference to study morphine-induced memory, we demonstrated that chemogenetic inhibition of VTA-DH projections decreased morphine-induced place preference and partly reversed the effects of SNI on mechanical nociceptive threshold. These studies begin to elucidate novel circuit mechanisms of chronic pain and opioid addiction.

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Poster

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Topic: G.02. Motivation

Support: JSPS KAKENHI Grant Number 15K18355

Title: Preparatory activity of nigral dopamine neurons supports flexible choice behavior

Authors: *K. TAO, S. FUJISAWA
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Abstract: Although secreted dopamine in striatum has been shown to represent motivation vigor and temporally discounted future reward, the underlying single cell activity in fine time-scale remains unclear. Here we show, by extracellular recording from the optogenetically identified dopamine (DA) neurons in substantia nigra pars compacta (SNc) while head-fixed mice were performing probabilistic reversal learning task, that DA neurons were heterogeneous in terms of reward and action encoding. A group of DA neurons encoding reward prediction error also exhibited outcome history-dependent activity during preparatory period and inter-trial interval. Multiple regression analysis revealed that the activity preceding each choice reflected a difference between estimated values of possible actions. Optogenetic perturbation of DA activity during preparatory period biased following choice. These results suggest that not only reinforcing but also preparatory DA activity has a causal role upon memory-guided decision making.

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Poster

072. Dopaminergic Reward Systems

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Topic: G.02. Motivation

Support: NWO VICI Grant # 453-14-015

Title: Dopamine and costly working memory contributions to stimulus-response learning

Authors: *A. WESTBROOK^{1,2,3}, R. VAN DEN BOSCH², B. LAMBREGTS², L. HOFMANS², D. PAPADOPETRAKI², J. MÄÄTTÄ², A. G. COLLINS⁴, M. J. FRANK⁵, R. COOLS^{2,3}

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Abstract: Stimulus-response learning can be accomplished entirely via reinforcement learning: phasic dopamine signals training striatal synapses to reflect incremental evidence over multiple encounters. Yet, recent work has demonstrated complementary, prefrontal cortex-based working memory contributions to the learning process (Collins & Frank, 2012; 2018). Intuitively, working memory affords rapid (e.g. one-trial) learning, but is limited by both the amount of information that can be maintained, and maintenance duration. Interestingly, working memory may also be costly, reflecting subjective cognitive effort. After stimulus-response learning, participants report rewarded stimuli as less rewarding, controlling for actual reward statistics, when they were learned in the context of large versus small working memory demands (Collins, Albrecht, Waltz, Gold, & Frank, 2017). In this study, we test the hypothesis that dopamine

mediates the degree to which cognitive effort is subjectively costly (Westbrook & Braver, 2016) and thus the degree to which people rely on working memory during stimulus-response learning. N = 100 participants were recruited to complete a recent paradigm (Collins & Frank, 2012) isolating working memory contributions in a multi-session, double-blind, placebo-controlled, pharmacopET study in which we measure baseline dopamine synthesis capacity with [18F]DOPA, and separately manipulate dopamine with methylphenidate, and antagonize D2 receptors with sulpiride. In a preliminary analysis (N = 35), we replicate the prior behavioral result that participants reliably pick stimuli as more rewarding if they, incidentally, were rewarded more during stimulus-response learning. Critically, we also replicate that participants find stimuli less rewarding when learned in the context of high working memory demands, supporting the hypothesis that working memory mechanisms are costly. A first analysis of PET data, blind to drug status, did not find that dopamine synthesis reliably predicted individual differences in the degree to which working memory demands discount perceived reward values. We describe implications of these results as well as on-going work to test whether reliance on working memory is sensitive to effort costs, and whether this is modulated by striatal dopamine synthesis capacity, and dopamine drug status.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.19/UU13

Topic: G.02. Motivation

Title: Dopamine D1 and D2 receptor mediation of neutral-valence learning

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Abstract: The neurotransmitter dopamine has been heavily implicated in reward-related learning and motivational processes, making it of key interest in the study of addiction and other motivational and emotional disorders. Recent evidence points to at least a partial dissociation in

the roles of distinct dopamine receptor subtypes, with dopamine D1 receptors (D1R) appearing critical for learning predictive relationships between contingent events in general, and dopamine D2 receptors (D2R) being involved more in motivational aspects of learning and performance. This idea was explored further in the present research, using a sensory preconditioning procedure that is able to isolate learning processes from motivational considerations. In Stage 1 of this task rats are exposed to pairings between 2 neutral stimuli (S2-S1). In Stage 2, S1 is then paired with a mild foot-shock (S1-Shock). The amount that was learned about the S2-S1 relationship can then be assessed by measuring fear to S2 (which was never directly paired with shock). Experiment 1 comprised a control study designed to confirm that responding to S2 at test is a function of the learned associations between both S2 and S1, and S1 and Shock. 24 Long-Evans rats were randomly allocated to one of three groups ($n = 8$; 4M and 4F) that either received paired or unpaired presentations of stimuli during Stage 1 and/or 2 (Paired-Paired; Paired-Unpaired; Unpaired-Paired). In Experiment 2, all rats ($N = 56$; 28M and 28F Long-Evans) received paired stimulus presentations in both Stage 1 and 2. To examine the importance of D1R and D2R for S2-S1 learning, rats in each group ($n = 8$) received SC injections of either a D1R antagonist (SCH39166; High, Mid, or Low dose), D2R antagonist (Eticlopride; High, Mid, or Low), or Saline, prior to Stage 1 training. Freezing at test was scored by 2 independent observers, one of whom was blind to experimental conditions. Where there was any discrepancy, this was resolved in favour of the blind observer. Results indicate that activity at both dopamine D1R and D2R is critical for neutral-valence learning. This is consistent with prior reports regarding the role of phasic dopamine activity (targeting D1R) in reward learning, but additionally indicates that the role of D2R also extends beyond relationships that involve motivationally salient events.

Disclosures: S. Roughley: None. S. Killcross: None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.20/UU14

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Title: Effect of inactivating nigrostriatal projections on sensitivity to outcome devaluation during sign-tracking behavior

Authors: *K. A. AMAYA, W. S. TACKETT, S. F. OHAZURUIKE, K. S. SMITH
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Abstract: Appetitive sign-tracking is a phenomenon involving the development of a conditioned response (CR) to cues (CS) that are predictive of rewards (US). For example, rats will interact with a lever cue by sniffing, biting, and pressing the lever while it is presented, then, only after the cue is withdrawn, will they proceed to the food delivery area. Thus, this behavioral model is well-suited to study the neural mechanisms of normal and excessive motivational attraction to reward-paired stimuli. Recent reports have indicated that appetitive sign-tracking is resistant to nausea-induced outcome devaluation, which is interesting because this is a hallmark test of habitual behavior in instrumental paradigms (Adams, 1981; Morrison et al., 2015; Smedley and Smith, 2018). Further, instrumental habit formation is critically dependent on a functional nigrostriatal dopaminergic system (Faure et al., 2005). With this background information, we investigated the role of the nigrostriatal dopamine system with respect to the development of outcome devaluation insensitivity during acquisition of the conditioned response during sign-tracking training. To do this, we used designer receptors exclusively activated by designer drugs (DREADDs) to inhibit of these projections throughout training. Following training, we conducted outcome devaluation by pairing the outcome with lithium chloride solution, then subsequently assessed whether sign-tracking persisted in rats that had these projections off-line previously. Our initial findings indicate that sign-tracking following outcome devaluation persists. This result preliminarily suggests that the 'habitual' nature of sign-tracking might not require nigrostriatal dopamine.

Disclosures: **K.A. Amaya:** None. **W.S. Tackett:** None. **S.F. Ohazuruike:** None. **K.S. Smith:** None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

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Program #/Poster #: 072.21/UU15

Topic: G.02. Motivation

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Title: Dorsal, but not ventral striatal dopamine mediates the effect of gambling disorder on compulsivity during reversal learning

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Neurosciences de Lyon, INSERM-CNRS, Lyon, France; ⁵Radiology and Nuclear Med., ⁶Psychiatry, Radboudumc, Nijmegen, Netherlands; ⁷E O Lawrence Berkeley Natl. Lab., Berkeley, CA; ⁸Helen Wills Neurosci Inst., Univ. of California, Berkeley, CA

Abstract: Background: Gambling disorder is characterized by compulsive gambling. Besides playing an important role in addiction, dopamine - especially in the dorsal striatum - has also been implicated in compulsivity. Recently we found evidence for higher striatal dopamine synthesis capacity in individuals with gambling disorder compared with controls. Here we test the mediating role of dorsal striatum (DS) and ventral striatum (VS) dopamine synthesis capacity in compulsivity.

Methods: We quantified compulsivity in terms of perseverative errors during a probabilistic reversal learning paradigm and combined this with FDOPA-PET to measure dopamine synthesis capacity (Ki values) in 14 controls and 12 pathological gamblers. We employed mediation analyses (using Lavaan in R and bootstrapping (n=5000)), including diagnosis (gamblers versus controls) as a predictor, and DS or VS Ki values as mediators. Furthermore, we directly compared the mediating role of the DS versus VS on predicting these outcome measures.

Results: The mediation model with DS Ki values was significant: diagnosis predicted perseverative errors (p<0.005), diagnosis also predicted DS Ki values (p<0.001), which in turn predicted perseverative errors (p<0.001). In addition, the indirect effect of diagnosis on perseverative errors via DS Ki was significant (p<0.007). The same model with VS Ki values was not significant, and a direct comparison of the two models indicated a significant difference in the mediation effect of DS versus VS Ki values on perseverative errors (p<0.015).

Conclusions: Our mediation analyses indicate that dopamine synthesis capacity specifically in the DS, and not the VS mediates the relationship between gambling disorder and compulsive, perseverative behavior.

Disclosures: **R.J. van Holst:** None. **G. Sescousse:** None. **T. van Timmeren:** None. **H.E. Den Ouden:** None. **M. Janssen:** None. **A.S. Berry:** None. **W.J. Jagust:** None. **R. Cools:** None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.22/UU16

Topic: G.02. Motivation

Support: OFT/NIMH/NIH

Title: Chemogenetic inactivation of amygdala affects reinforcement learning in rodents

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Abstract: The behavioral process of learning the values of actions and objects is known as reinforcement learning (RL). RL is often studied in the context of two-armed bandit tasks, in which subjects choose between a pair of options. By integrating choice outcomes over trials, they can learn which option is more rewarding to guide future choices. In our study, we implemented a rodent two-armed bandit task using a touchscreen platform in which animals initiated a trial by nose-poking a food magazine located opposite the visual display. Two different geometric objects were then presented on the left and right side of the touchscreen. The locations of these objects varied trial-to-trial. The animals approached the touchscreen and made a choice by nose-poking one of the two visual objects. A response to the correct object was rewarded with 10% sucrose liquid reward. A response to the incorrect object was not rewarded and animals were subjected to a corrective procedure in which the house light was turned on for 5 seconds after the incorrect choice was made. Trials were always followed by a 5 second intertrial interval during which the animals were in complete darkness. Animals were trained on this task for 50 days prior to the experimental manipulations. We used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to evaluate the contribution of the amygdala to this choice behavior. Three weeks after infusing pAAV8-hSyn-hM4D(Gi)-mCherry in 7 animals (cohort n=13) and pAAV8-hSyn-EGFP in 6 animals, as controls, all animals were tested in the bandit task for 60 minutes for 5 consecutive days. They performed a total of 3 object pair discriminations, with a new object pair introduced each week. On day 2 of each discrimination, all animals received i.p. injections of either clozapine (0.5mg/kg), which is an agonist of the DREADD receptor, or vehicle (PBS) and were tested 30 minutes after injection. Preliminary results suggest that there was no significant difference between task performance for clozapine vs vehicle sessions. Future experiments will explore the underlying circuit for these behaviors as well as alternate approaches to study the amygdala's role in reinforcement learning.

Disclosures: G.M. Zabala-Aleman: None. Y. Chudasama: None. B. Averbek: None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.23/UU17

Topic: G.02. Motivation

Title: Predictive reward signals of dopamine neurons are controlled by attentional states

Authors: *W. PAN, J. T. DUDMAN

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Abstract: The midbrain dopamine prediction signals are evoked by sensory stimuli predicting reward. Recent studies have showed that the responses of dopamine neurons to the prediction cues depend on subjective perception. However, the mechanisms of this feature of dopamine neuron activities are unknown. We used an attention-uncertainty cues task to test if the dopamine neuron responses are controlled by attentional state. The results showed that dopamine responded to the attention signals and the following uncertainty reward cues in correct behavioral “hit” (get reward) trials, but did not respond to the attention signals and the reward cues in behavioral “miss” (miss reward) trials. The non-dopamine neurons in the midbrain area generally respond to sensory stimuli with earlier latencies than that of dopamine neurons. In this task we recorded that some non-dopamine neurons with earlier latency also stopped responding to the attention signals in the behavioral “miss” trials. All these suggested that the earlier process of the subjective perception is important to finally activate the dopamine neurons and attention state may gate the dopamine neuron responses to sensory stimuli.

Disclosures: W. Pan: None. J.T. Dudman: None.

Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.24/UU18

Topic: G.02. Motivation

Title: Adolescent high fructose corn syrup exposure disrupts learning and motivational processes into adulthood

Authors: S. M. KRUGEL¹, J. BRITTEN¹, D. L. RAMOS, Jr.¹, N. C. DYANICK¹, K. D. LASHER¹, R. P. DALY¹, T. BERNICKER¹, S. E. YOHN², D. F. WERNER³, *J. L. SANTERRE-ANDERSON¹

¹Kings Col., Wilkes Barre, PA; ²Vanderbilt Univ., Nashville, TN; ³Psychology and Behavioral Neurosci., Binghamton Univ., Binghamton, NY

Abstract: Adolescence is a critical period of development, whereby exposure to drugs of abuse can have long-lasting consequences on proper neural maturation. In addition to classic drugs of abuse, dietary choices, such as sugar and high fructose corn syrup (HFCS) have a definitive link to not only the obesity epidemic, but deficits in proper behavioral development. Problematically, HFCS consumption is dramatically increasing, with adolescents consuming 5 times the recommended daily allowances of sugar. Therefore, we determined the long-term effects of adolescent HFCS consumption on motivation and learning ability into adulthood, and examined potential molecular correlates. Adolescent male Sprague-Dawley rats (postnatal day 21-54; P21-P54) were given free access to one experimental bottle containing either 11% HFCS (HFCS, n=6) or tap water (control, n=5) and one control bottle containing plain tap water. Fluid intake,

chow consumption and body weight were monitored throughout the exposure period. Following the exposure period, HFCS was replaced with plain tap water for the remainder of the experiment. Three weeks following HFCS cessation (P78), learning and motivated behaviors were ascertained using an effort-related T-Maze paradigm. Following behavioral testing, brains were collected for Western Blot analysis. Preliminary data suggests that adolescent rats exposed to HFCS did not gain excessive weight compared to controls, likely due to a compensatory reduction in chow consumption. Importantly, preliminary data indicates that HFCS treated rats acquired a spatial learning task at a significantly slower rate compared to controls ($p < 0.05$), indicative of deficits in learning. Further, behaviors requiring a high motivational output showed a trend towards impairment following HFCS exposure ($p < 0.06$). In addition to behavior, ongoing experiments are investigating dopamine D2 and protein kinase G levels. Taken together, these results suggest that exposure to HFCS during adolescence can result in maladaptive behaviors, which persist into adulthood.

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Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.25/UU19

Topic: E.03. Basal Ganglia

Support: Gayle & Ben Batey Neuroscience Fund
MARC U STAR NIH 5T34GM118212

Title: Effect of a high fat diet on dopaminergic D2 antagonist-induced hypokinesia and agonist-induced stereotypies in rats

Authors: *S. VILLARREAL, N. RAMIREZ, A. HUSSAIN, C. GREENE, I. C. SUMAYA
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Abstract: Dopamine is a catecholamine neurotransmitter released in the brain playing a number of roles in both humans and nonhuman animals. Most notably, dopamine mis-signaling has been implicated in such human diseases as Parkinson's disease where there is a lack of dopamine and in schizophrenia where there is too much of the neurotransmitter. Dopamine's effects are mediated by the binding to its receptors which include the five subtypes, D1, D2, D3, D4, and D5. In the case of Parkinson's disease, pharmacological agents work to increase dopamine, while in the case of Schizophrenia drugs serve to block and reduce dopamine. Activity at the D2 receptor sites are a major player in mediating the effects of these drugs. Relevant to our research

are the recent findings that high fat serves to deplete dopamine in the substantia nigra and the striatum (Morris et al., 2010), the major players in motor responses. Based on these findings, the purpose of the current experiments was to provide first time behavioral data investigating the effects of high fat on the D2 system by treating rats with a D2 antagonist, haloperidol (HAL: 1 mg/kg ip), serving to inhibit dopamine release, and the D2 agonist, apomorphine (APO: 1 mg/kg ip), facilitating the release of dopamine. Also, based on previous work done in our lab finding that enriched environments served to counteract the negative effects of high fat in cognitive domains (Sumaya et al., 2015), we were also interested in investigating the possible effects of environmental enrichment on motor domains after treatment with HAL, or APO. Male Sprague-Dawley albino rats were either fed a low fat (10% fat) or a high fat diet (45% fat) for a month then hypokinesia and stereotypies were measured. High fat served to dramatically counteract the effect of HAL (17.10 ± 4.37 s) as compared to the low fat group (1090 ± 238.50 s). Paradoxically, rats in the enriched environments fed high fat experienced high levels of hypokinesia (587.40 ± 203.82 s) suggesting enrichment reversed that effect. In contrast, for the agonist, high fat served to potentiate the effect of APO over time for both the standard and enriched environment as compared to the low fat. These data provide first time behavioral evidence that 1) high fat diets alter the D2 receptor dopamine system, and 2) these effects are differential based on agonism or antagonism of the D2 receptor system. Given these drugs are used in clinical populations, it is important to investigate the possible impact dietary intake may have on the efficacy of dopaminergic drugs. These results provide first time behavioral data showing high fat diets to interfere with the D2 dopamine receptor system.

Disclosures: **S. Villarreal:** None. **N. Ramirez:** None. **A. Hussain:** None. **C. Greene:** None. **I.C. Sumaya:** None.

Poster

072. Dopaminergic Reward Systems

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Program #/Poster #: 072.26/UU20

Topic: G.02. Motivation

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Title: Your offspring is what you eat: The impact of maternal CAF diet on the epigenetic control of dopaminergic-related genes during perinatal period

Authors: *M. F. ROSSETTI^{1,2}, R. SCHUMACHER^{1,2}, C. STOKER^{1,2}, G. LAZZARINO^{1,2}, M. ANDREOLI³, J. VARAYOUD^{1,4}, J. RAMOS^{1,2}

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Abstract: Dopamine is a neurotransmitter crucial for motor, motivational, and reward-related functions of the central nervous system. Our aim was to determine the effect of a palatable maternal diet on the transcriptional regulation of genes involved in dopaminergic pathways during perinatal period in the offspring. Wistar female rats received a diet composed of standard chow (CON) and/or cafeteria “junk-food” (CAF) from weaning and during 120 days (N=10/group). After mating, dams were maintained on their respective diets. Female offspring from CON and CAF dams were sacrificed on embryonic day 21 (E21) and postnatal day 10 (PND10) (N=16/group). This experimental model allowed us to study the individual and combined effects of age (E21 vs. PND10) and maternal diet (CON vs. CAF). Using micropunch techniques, ventral tegmental area (VTA) and accumbens nucleus (NAc) were isolated from offspring´s brains. Bioinformatic analysis of the promoter regions, mRNA quantification and methylation studies were done (N=8/group). Each sample was quantified in duplicate. Our results showed an increase in mRNA expression of tyroxine hydroxylase (TH), dopamine receptor (DRD) 1 and ghrelin receptor (GHSR) from E21 to PND10 in the offspring of CON fed-dams ($p<0.05$) and a decrease in methylation levels of its promoters in VTA and NAc ($p<0.05$). Maternal CAF diet did not affect gene expression in the studied areas in E21. However, a decrease in the transcription of TH, DRD2 and dopamine transporter (DAT) was reported in VTA in the offspring of CAF fed-dams at PND10 ($p<0.05$). The changes in TH, DRD2 and DAT expression were related to the methylation status of their promoter regions ($p<0.05$). In NAc, maternal CAF diet reduced DRD1 and DRD2 expression in the offspring at PND10 ($p<0.05$), although no alternations in methylation levels were detected. The present study shows that transcriptional regulation of dopamine-related genes is mediated by methylation mechanisms in developing rat brains. During this time, maternal nutrition environment is crucial and alterations in this pathway´s function could be established. These results provide novel insights into the mechanisms through which maternal “junk-food” diet can affect dopaminergic pathways in early postnatal development. Particularly important is the decline in the expression of DRD2 given its physiological implication on health diseases associated with obesity and addictions.

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Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.27/UU21

Topic: G.02. Motivation

Title: How sweet it is: Dissociating the 'wanting' and 'liking' of chocolate in humans

Authors: *A. MASTROIANNI, R. EIKELBOOM

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Abstract: Eating beyond homeostatic need was previously ascribed to a unitary construct, proportional to the pleasure experienced (Bindra, 1974). The incentive salience theory (IST) suggests that food reward has a dual nature and involves 'wanting' (motivational) and 'liking' (affective) components (W&L; Robinson & Berridge, 1993; 1998). Rodent work has found that W&L rely on separate neural mechanisms. Wanting is dependent on mesolimbic dopamine, while liking is not. There is mounting evidence that W&L can dissociate and differentially affect an animal's food behaviour (Berridge & Robinson, 2016). Human W&L findings have been less consistent (Havermans, 2011). This research explored if these components can be dissociated in healthy undergraduate students, focusing on the W&L of chocolate. **METHODS:** Two experiments (N=27 and 46) measured the W&L of chocolate before and after inducing sensory specific (through chocolate eating) or general satiety (through potato chip eating). Liking for chocolate was measured using taste ratings while consuming. Wanting for chocolate was measured using a modified willingness-to-pay procedure (WTP; Ziauddeen et al., 2014) and by asking participants to rate their desire to eat more chocolate. Experiment 2 included a WTP manipulation, looking at immediate vs. future chocolate wanting. It was expected that chocolate satiety would greatly decrease wanting and slightly decrease liking, showing a dissociation. We expected immediate wanting to decrease more than future wanting as a result of sensory specific satiety. **RESULTS:** WTP wanting was not significantly changed by the experimental manipulations. It is unclear if the WTP procedure measured incentive salience wanting or a cognitive form of wanting that taps into expected pleasantness (predictions about liking; Pool et al., 2016). Our further work will focus on improving wanting methodology. Liking and wanting more chocolate significantly decreased in the chocolate eating groups, but not in the potato chip groups. Wanting more chocolate decreased significantly more than liking, providing evidence to support our hypothesis and the IST. Our findings shed some light into the intricacy of human W&L.

Disclosures: R. Eikelboom: None.

Poster

072. Dopaminergic Reward Systems

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 072.28/UU22

Topic: G.02. Motivation

Support: NWO Vici 453-14-015

Title: Dopamine synthesis capacity as a predictor of individual differences in behavioral and neural responses to methylphenidate

Authors: *R. VAN DEN BOSCH^{1,2}, B. I. H. M. LAMBREGTS¹, L. HOFMANS^{1,2}, D. PAPADOPETRAKI^{1,2}, J. I. M. MÄÄTTÄ^{1,2}, A. WESTBROOK^{3,1,2}, R. COOLS^{1,2}

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Abstract: Individuals vary considerably in their response to the dopamine (and noradrenaline) transporter blocker methylphenidate, posing a major challenge for psychiatry. It has been proposed that individual differences in drug response reflect variation in baseline dopamine function in the striatum. Preliminary small sample studies indicate, for example, that dopamine receptor agents have diametrically opposite effects on learning from rewards and punishments, and associated striatal BOLD signal in participants with (putatively) high versus low baseline levels of striatal dopamine (Cools et al., 2009; Van der Schaaf et al., 2014). Here, we examine the relationship between dopamine synthesis capacity and striatal responses in a reinforcement learning task, and the potential of this relationship to index baseline-dependent drug effects on behavioral and neural responses. In a large sample of young healthy participants (N = 100), we combined PET, pharmacology, fMRI and a reversal learning task in which unexpected rewards or punishments signal reversals of response contingencies. In this placebo-controlled, double-blind, cross-over design, participants performed the reversal learning task while being scanned using fMRI on three occasions: once on placebo, once on methylphenidate (20mg) and once on the selective dopamine receptor antagonist sulpiride (400mg). In a separate session, participants underwent an [18F]DOPA PET scan to quantify their dopamine synthesis capacity. Critically, the study is designed to assess individual differences in effects of methylphenidate, and how they depend on baseline dopamine synthesis capacity, to be tested following drug de-blinding. To that end, we hypothesize that synthesis capacity is positively correlated with (i) learning from unexpected rewards versus unexpected punishments, and (ii) fMRI markers of reward- versus punishment learning. Furthermore, fMRI allows us to determine the locus of these effects, in the context of a reinforcement learning task, and adjudicate between specific predictions implicating the basal ganglia, the prefrontal cortex, or both. Preliminary, exploratory analysis of a subset of the data (N = 40), blind to drug status and averaged over sessions, shows that greater dopamine

synthesis capacity is associated with greater BOLD signal related to reward- vs punishment learning bilaterally in a cluster of striatal voxels, uncorrected for multiple comparisons at $p < 0.001$. An effect of baseline dopamine synthesis capacity on reversal learning in the striatum provides a key metric for baseline-dependent drug effects after de-blinding of drug coding upon completion of data collection.

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Poster

072. Dopaminergic Reward Systems

Location: SDCC Halls B-H

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Program #/Poster #: 072.29/VV1

Topic: E.03. Basal Ganglia

Support: NIH Grant GM083883
NIH Grant DA033877

Title: Ketamine-induced locomotor activity in preweanling and adolescent male and female rats: Role of the dopamine system

Authors: *A. E. MORAN, M. G. APODACA, T. J. BAUM, V. GOMEZ, C. A. CRAWFORD, S. A. MCDUGALL
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Abstract: Ketamine is a dissociative anesthetic, a quick-acting treatment for major depression, and an illicit drug used for recreational purposes. Considering its wide range of behavioral effects, it is not surprising that ketamine has multiple mechanisms of action. Ketamine is a non-competitive NMDA receptor antagonist that may produce some of its anesthetic, psychotropic, and anti-depressive effects via actions involving the dopamine (DA) system. In fact, the ability of ketamine to robustly increase the locomotor activity of adult rats is often ascribed to enhanced DA neurotransmission. To further study this potential ketamine-DA interaction, male and female preweanling and adolescent rats were treated with vehicle, a DA depleting agent (1 or 5 mg/kg reserpine), or a DA synthesis inhibitor (2×200 mg/kg α -methyl-DL-p-tyrosine methyl ester hydrochloride, AMPT) at appropriate time points prior to an acute injection of saline or ketamine (5, 10, 20, or 40 mg/kg, ip). Locomotor activity was then measured for 2 h. In addition to assessing behavior, dorsal striatal samples from separate groups of vehicle-, reserpine-, and AMPT-treated rats were assayed for DA using HPLC. Results showed that ketamine increased the locomotion of male and female preweanling and adolescent rats, although ketamine's locomotor activating effects were less pronounced in male adolescents. The DA synthesis inhibitor AMPT significantly reduced DA levels in the dorsal striatum by 78% and attenuated

ketamine-induced locomotor activity of both age groups. The effects of reserpine were more complex, as 1 mg/kg reserpine caused only a 45% reduction in the DA content of adolescent rats and had minimal effects on ketamine-induced locomotor activity. On the other hand, 5 mg/kg reserpine produced an 87% reduction in dorsal striatal DA levels and significantly decreased the ketamine-induced locomotion of preweanling and adolescent rats. In summary, these results show that ketamine produces substantial locomotor activity in female adolescent rats and preweanling rats (both sexes), while male adolescent rats exhibit a lesser amount of ketamine-induced locomotion. Despite these age and sex differences, reserpine (5 mg/kg) and AMPT (2 × 200 mg/kg) significantly reduced the ketamine-induced locomotor activity of male and female preweanling and adolescent rats. These results are consistent with the hypothesis that ketamine's locomotor activating effects are mediated through a dopaminergic mechanism.

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Poster

072. Dopaminergic Reward Systems

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Topic: E.03. Basal Ganglia

Support: NIH Grant GM083883
NIH Grant DA033877

Title: Ketamine differentially affects the locomotor activity of male and female rats across ontogeny: Role of ketamine pharmacokinetics

Authors: *V. GOMEZ, G. I. RAMIREZ, G. I. PARK, B. C. ADAME, C. A. CRAWFORD, S. A. MCDUGALL

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Abstract: Although ketamine is typically thought of as a dissociative anesthetic, this non-competitive NMDA receptor antagonist causes substantial amounts of locomotor activity when administered at low to moderate doses. Interestingly, ketamine-induced locomotor activity varies according to both age and sex. The reason for these age- and sex-dependent differences is uncertain, but it is possible that ketamine pharmacokinetics is responsible. To further examine the behavioral actions of ketamine, male and female preweanling [postnatal day (PD) 20], adolescent (PD 30 and PD 40), and adult (PD 80) rats were injected (ip) with 80 mg/kg ketamine and locomotor activity was measured continuously for 280 min. In a separate experiment, the dorsal striata and hippocampi of male and female preweanling, adolescent, and adult rats were removed bilaterally at 10 time points (0-360 min) after ketamine (80 mg/kg) administration. Peak

brain levels and half-life of ketamine and norketamine were determined using HPLC. In general, ketamine affected the locomotor activity of female rats similarly across the ages tested, as peak locomotion occurred 90 min (PD 20 and PD 30), 100 min (PD 40), and 120 min (PD 80) after ketamine treatment. With the exception of the youngest age group, ketamine stimulated less locomotor activity in male rats than female rats. Moreover, peak locomotor activity was reached more quickly in male adolescent and adult rats than female rats. Specifically, peak locomotion of male rats occurred 50 min (PD 30), 30 min (PD 40), and 40 min (PD 80) after ketamine treatment, which is 1.8 to 3.3 times more quickly than for female rats of the same age. Overall, ketamine half-life in brain varied according to both age and sex, and was generally reflective of the locomotor activity data. More specifically, the ketamine half-life of female rats remained stable across the four age groups (PD 20-PD 80); whereas, the ketamine half-life of male rats declined in a step-wise and progressive manner from PD 20 to PD 80. Thus, the ketamine half-life of male and female rats did not differ on PD 20, while the ketamine half-life of adult female rats (43.2 min) was over 2.4-fold greater than the half-life of adult male rats (17.8 min). In addition, peak ketamine values were significantly greater in older female rats (PD 40 and PD 80) than male rats of the same age. In summary, these results show that ketamine-induced locomotor activity varies according to both age and sex: an effect that may be explained by differences in ketamine pharmacokinetics.

Disclosures: G.I. Ramirez: None. G.I. Park: None. B.C. Adame: None. C.A. Crawford: None. S.A. McDougall: None.

Poster

073. Motivation: Cortical Neurocircuitry

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Program #/Poster #: 073.01/VV3

Topic: G.02. Motivation

Support: NIH Grant AG044862

Title: Increased extracellular free-water in the frontopolar cortex predicts cognitive fatigability in older adults

Authors: *S. E. BURKE¹, I. B. H. SAMUEL¹, Q. ZHAO¹, S. SIEGEL¹, J. CAGLE¹, B. KLUGER², M. DING¹

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Abstract: Cognitive fatigue is a severely disabling condition of extreme mental exhaustion in older adults that can lead to disability and increased mortality. Whereas perceive cognitive fatigue is widely assessed by instruments such as the Fatigue Severity Scale (FSS), cognitive fatigability, which characterizes the propensity to become fatigued for a given intensity and

duration of cognitive activity, has yet to be operationalized. We have recently proposed a method to measure cognitive fatigability in the context of prolonged performance of a cognitively demanding task. Here we examine its neural substrate. 35 older adults between the ages of 60 to 90 were recruited to perform a cued Stroop task for two hours. Cognitive fatigue levels were assessed every 20 min during the task. The rate of cognitive fatigue increase was defined as cognitive fatigability. On a separate visit, the same participants underwent diffusion magnetic resonance imaging (MRI). Applying a recently proposed algorithm for estimating free-water from diffusion MRI, we found that higher free water in the right frontopolar cortex (FPC), but not anterior cingulate cortex or dorsal lateral prefrontal cortex, predicted higher cognitive fatigability. Interpreting higher free water as an indicator of more severe neuroinflammation, these results suggests that aging-related neuroinflammation in the brain's motivational circuit, leading to edema in cortical gray matter, underlies cognitive fatigability.

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Poster

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Topic: G.02. Motivation

Support: NSF GRFP to MTV
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NIH MH087610 to TE
NIH MH087610 to TE

Title: Functional brain networks linking motivated anticipation to subsequent memory

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Abstract: High levels of curiosity, like high reward, facilitate increased memory encoding success. In terms of underlying neural circuitry, cues predicting high-curiosity outcomes elicit activation in mesolimbic dopamine circuitry supporting memory, and it has been shown that hippocampal activation at cue predicts subsequent memory success for high-but not low-curiosity information. However, how this high-curiosity state gets carried over time from the cue to influence subsequent memory success, and how brain regions at a brain-wide network level may be involved, remains to be investigated. To this end, we designed an fMRI study in which

subjects were presented with trivia questions to manipulate evoked curiosity, were required to wait for an anticipatory delay, and then were shown the answers. To disambiguate curiosity-driven anticipation from response preparation, we required subjects to make a button press in order to see the answer on half of the trials. After the scan, participants received a surprise recall test for the answers. While both curiosity and response contingency boosted memory, there was also an interaction whereby the action contingency only boosted memory for low-curiosity questions. To identify functional brain networks that carry motivational state to influence subsequent memory, we took a data-driven approach. We used independent components analysis (ICA) first to identify putative functional brain networks, agnostic to any behavior or task events. Next we queried these networks for anticipatory activity that related the motivational context (curiosity and/or response-contingency) set at the time of question to subsequent memory for the answer. Our analyses revealed two relevant networks. These networks both partially mediated the effects of motivational state on memory success, and the anticipatory activity of one of the networks was correlated with VTA activation at the question. Our results suggest that motivational anticipatory state is carried at the network level to influence subsequent learning and memory.

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Poster

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Topic: G.02. Motivation

Support: Fondation pour la Recherche Medicale (FRM Grant)

Title: Investigation of the role of the ventro-medial prefrontal cortex local morphology in its functional organization

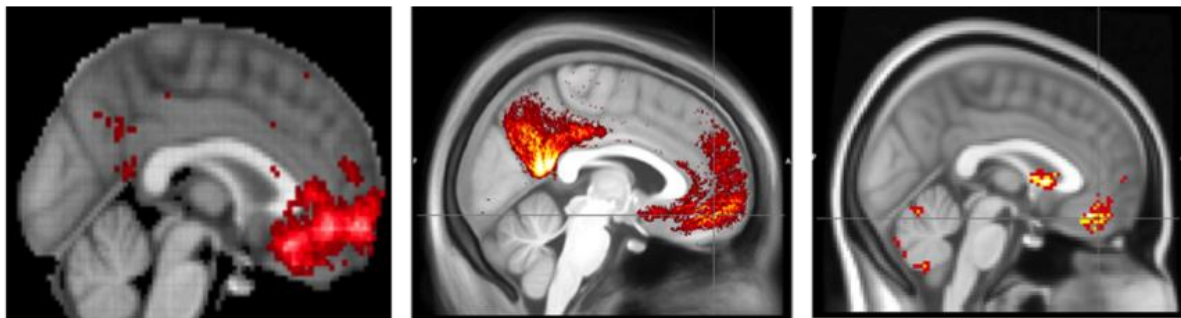
Authors: *A. LOPEZ-PERSEM¹, C. AMIEZ², J. SALLET¹

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Abstract: In humans, the ventro-medial prefrontal cortex (vmPFC) is assumed to be a key region for supporting decision-making processes. It is in particular associated with the ability to assign values to options that we are facing in our everyday life choices. On the other hand, the vmPFC is also one of the main hub of the Default Mode Network, a network classically activated during resting-state. However, the term “vmPFC” does not refer to a specific anatomical delineated brain area. Functional neuroimaging studies that are classically based on statistical

inferences established on the average brain activity of a group of subjects showed that “vmPFC” is used to label a large portion of the prefrontal cortex. It comprises various cytoarchitectonic subdivisions such as Brodmann area 10, 14, 25 and 32 and vmPFC boundaries are debated. Moreover, the fact that the classic neuroimaging approach is to average results across subjects in the MNI referential induces a glossing over of the interindividual variability of the morphological sulcal patterns of the vmPFC.

In our study, using a dataset of 57 subjects from the Human Connectome Project for which anatomical MRI, resting-state MRI and functional reward-related task MRI data are available, we provide a precise description of the vmPFC sulcal patterns. We first show that sulcal patterns can vary either in terms of presence/absence of sulci but also in terms of shape or relative position to one from another. Importantly, we found that the position of the main sulci influences differentially the localisation of the vmPFC peak in the reward-related fMRI session and in the Default Mode Network identified in the resting-state MRI session. Those results are critical for the investigation of the function of the vmPFC. Indeed, they reveal that the brain area that we label “vmPFC” in two different contexts might be two distinct functional areas which initially appear to be the same due to averaging effects. In conclusion, we show that taking into account the variability in sulcal patterns might be essential to guide the interpretation of neuroimaging studies of the vmPFC.



‘vmPFC’ label on
Neurosynth

‘vmPFC’ in the
Default Mode network

‘vmPFC’ in a reward-
related task

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Poster

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Support: NIH 1R01NS092894-01
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NYS SCIRB C30600GG
NYS SCIRB C030838GG

Title: Reward and aversion representation in the primary somatosensory, primary motor, and dorsal premotor cortices of non-human primates completing a motor task

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Abstract: Signals of reward and aversion have been recorded in a number of areas in the brain, from the midbrain to the cortex. This work explores how these variables are represented in the hand and arm regions of the primary motor cortex (M1), primary somatosensory cortex (S1), and dorsal premotor cortex (PMd). Two non-human primates (NHPs) were trained to complete a gripping task on a virtual robotic arm, where the animal manually gripped and held a given level of force for a specified period of time. Prior to each trial, visual cues were displayed to inform the NHP if the trial would result in a juice reward if completed successfully, a punishment consisting of a five-second timeout if completed unsuccessfully, or no reward or punishment, where the task would move immediately to the next trial. Subsets of trials with no cues and with catch trials, where a cue was presented but no reward or punishment delivered, were included to investigate reward and punishment prediction and error. Multiple levels of reward and punishment were incorporated to investigate how reward and punishment magnitude were represented in these regions, and how the interplay between the two was represented as motivation and/or value. Investigating the intricacies of these signals in M1, S1, and PMd will allow future brain-machine interfaces (BMI) to capture the breadth of these signals in a limited number of cortical regions that also contain sensorimotor information, rather than requiring multiple implants in multiple regions. Taking full advantage of the range of information in these regions will be useful in creating algorithms for more robust, nuanced, and naturalistic BMI control.

Disclosures: **J.P. Hessburg:** None. **A. Tarigoppula:** None. **D.B. McNiell:** None. **J.T. Francis:** None.

Poster

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Topic: G.02. Motivation

Support: KAKENHI Grant 16H06405

Title: Thiamine tetrahydrofurfuryl disulfide promotes voluntary locomotor activity through dopaminergic activation in the medial prefrontal cortex

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Abstract: A physically active lifestyle is associated with better health in body and mind, and it is urgent that supporting agents for such lifestyles be developed. In rodents, voluntary locomotor activity as an active physical behavior may be mediated by dopaminergic neurons (DNs), and, in particular, DNs from the ventral tegmental area that project into the medial prefrontal cortex (mPFC) are involved in the reward system. Antihypnotic agent injection induces dose-dependent dopamine release in the mPFC and increases voluntary locomotor activity through the dopamine D1 receptor in rats. These data suggest that DNs in the mPFC are a potential target of agents that induce physical activity. Although we must be careful of addiction induced by drugs such as anti hypnotic agent, thiamine tetrahydrofurfuryl disulfide (TTFD), a popular thiamine derivative, is a potential agent for the activation of DNs without severe side effects. TTFD is more rapidly absorbed than thiamine and it is metabolized into thiamine and its phosphorylated esters. The local injection of thiamine phosphorylated esters into the rat striatum increases dopamine release, suggesting a possible role of TTFD on DNs in the brain. However, the effects of TTFD on the brain, particularly on the DNs in the mPFC, and voluntary locomotor activity remain unclear. We thus hypothesized that TTFD promotes voluntary locomotor activity via DNs in the mPFC. To test the present hypothesis, we employed a rat model of acute TTFD (50 mg/kg) injection, voluntary locomotor activity detection with infrared radiation, and *in vivo* microdialysis. First, we investigated the effect of acute TTFD i.p. injection on voluntary locomotor activity in rats in a normal cage. Acute i.p. administration of TTFD enhanced rat voluntary locomotor activity in a normal cage. Next, *in vivo* microdialysis revealed that TTFD-enhanced voluntary locomotor activity was synchronized with dopamine release in the mPFC. Third, we examined the inhibitory effects of dopamine D1 and D2 receptors on voluntary locomotor activity after TTFD injection. Rats were infused with a D1 antagonist (SCH23390) or a D2 antagonist (sulpiride) into the mPFC at a flow rate of 2 μ l/min via the microdialysis probe. Antagonism of the dopamine D1 receptor, but not D2 receptor, in the mPFC fully suppressed TTFD-enhanced voluntary locomotor activity. Finally, we assessed the effect of acute TTFD i.p. injection on voluntary running distance in a wheel cage. We found a TTFD dose-dependent increase in voluntary wheel running. Our findings demonstrate that DNs in the mPFC mediate TTFD-enhanced voluntary locomotor activity, suggesting the potential of TTFD to induce active physical behavior.

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Poster

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Topic: G.02. Motivation

Support: NIH Grant NS058280

UCLA Division of Life Sciences Recruitment and Retention Fund

Title: Mediation of effort-based choice and miniaturized fluorescence microscopy calcium imaging in rat anterior cingulate cortex

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Abstract: Effort is a cost that must be overcome to acquire rewards, and organisms must make cost-benefit analyses in choosing between rewards of different value. While much is known about the striatal neuropharmacology of effort-based choice, less work has examined other brain regions, circuits, and neural correlates of choice between qualitatively different rewards (more preferred vs. less preferred). Rats were tested in an effort-based choice task where they could freely choose between lever pressing on a progressive ratio schedule for sucrose pellets and consuming freely available standard lab chow. We first sought to replicate effects of pharmacological basolateral amygdala (BLA) inactivation (Hart & Izquierdo 2017) and anterior cingulate cortex (ACC) lesion (Hart et al 2017) using a chemogenetic approach. Separate groups of rats were infused with 0.5 uL of AAV8-CaMKIIa-hM4D(Gi)-mCherry in either BLA or ACC to target specifically pyramidal neurons. CNO (3.0 mg/kg, i.p.) had no effect on choice in the BLA group. CNO decreased lever pressing in the context of choice in the ACC group. Importantly, these effects were not due to inability to lever press, decreased appetite, or changes in food preference. We showed that CNO had no effects in a cohort of null virus control animals. We next sought to determine the role of reciprocal connections between these regions. Rats were infused with a Cre-dependent DREADD virus (AAV8-CaMKIIa-DIO-hM4D(Gi)-mCherry) in ACC and a retrograde Cre-expressing virus (AAVretrograde-pmSyn1-EBFP-Cre) in BLA to target ACC-BLA projection neurons. CNO had no effect on choice behavior. To track the dynamics of choice on a second-by-second basis, rats were infused with a virus containing the fluorescent protein GCaMP6f in ACC followed by implantation of a GRIN lens for endoscopic imaging. We recorded calcium transients using custom-made miniaturized fluorescence microscopes in ACC during choice testing to determine whether high effort and low effort choice are represented in differential neuronal ensembles. Preliminary analyses indicate there are populations of task-engaged cells preferentially active during lever pressing, chow consumption,

or both. Taken together, these findings have implications in understanding methodological differences between traditional inactivation/lesion and cell-type specific chemogenetic silencing, and they uncover a previously unidentified neural correlate of effort-based choice between qualitatively different options.

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Poster

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Topic: G.02. Motivation

Support: NIMH R01 Grant MH074723
T32 GM007507

Title: Dissociable control of μ -opioid-mediated hyperphagia vs. food impulsivity across medial prefrontal, orbitofrontal, and agranular insular cortices in rat

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Abstract: Abnormalities in both prefrontal cortical function and opioid transmission have been implicated in dysregulated appetitive motivation and impulsivity, two components of psychiatric disorders with binge features (including binge eating disorder (BED)). Previously, we showed that μ -opioid receptor (MOR) stimulation in rat ventromedial prefrontal cortex (vmPFC) elicits hyperphagia and provokes an ‘impulsivity-like’ loss of control over food-seeking behavior. The present study was designed to map the frontal sites subserving μ -opioid-mediated hyperphagia and impulsivity, with the goal of determining possible site dissociations in the control of these behaviors. Using ultrathin microinjectors, small volumes (250 nl) of the selective MOR agonist, D-[Ala²,N-MePhe⁴, Gly-ol]-enkephalin (DAMGO; 0, 0.1, 0.3, 1.0 μ g) were infused bilaterally into the infralimbic (IL), prelimbic (PrL), ventromedial and ventrolateral orbitofrontal (VMO, VLO), and agranular insular (AI) cortex of male rats. DAMGO-induced effects on sucrose approach and intake, and inhibitory control in a sucrose-reinforced DRL task (which assesses the ability to advantageously withhold a prepotent lever-press) were assessed using a within-subjects design. DAMGO elicited hyperphagia when infused into IL, VMO, and AI cortices, with a notably large effect in AI cortex. The same doses of DAMGO failed to affect DRL performance in any site *except* IL cortex, where DAMGO robustly disrupted responding. Intra-PrL and intra-

VLO DAMGO produced no effects on any measure. These findings indicate that MOR-driven hyperphagia elicited from VMO and AI cortices are not sufficient to provoke food-motivated impulsive action in the presence of an intact IL cortex. IL-localized MOR signaling may disrupt a process (perhaps an action-selection or “filtering” process) that operates in parallel to motivational effects elicited in IL cortex and elsewhere. This functional insight into regional heterogeneity of cortical opioid actions may be important for understanding the etiology of BED, given that medial prefrontal cortex, insular cortex, MOR transmission, and dysfunctional dissociations between inhibitory control and motivation have all been implicated in this disorder.

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Poster

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Program #/Poster #: 073.08/VV10

Topic: G.02. Motivation

Title: Cortical parietal thickness and hippocampal volume are bidirectionally associated with executive function and impulsive externalizing behavior

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Abstract: Introduction

Examining human traits, which shape our behavior, may elucidate the relationship between brain structure and function with cognitive abilities and actions. The overarching domain of human cognitive abilities is referred to as executive function (EF). EF involves focusing or attending to stimuli, planning, self-regulation, and executing decisions. One trait that negatively relates to EF is impulsivity, an externalizing behavior that is related to risky decision-making, or not fully weighing possible risks of an action, typically due to selecting an immediate reward. Therefore, understanding the complexity of human traits allows for deeper insight into our behavior and consequently, certain behavioral and cognitive deficits associated with pathology.

Objectives

To explore possible relationships between structural brain morphometry and connectivity, and behavioral measures related to EF and impulsivity.

Methods

Sample: 85 adults (55 males, 30 females), 18-59 years of age (M = 33.5, SD =11.0) with anatomical (MPRAGE) and diffusion tensor imaging scans. Data were obtained from the Nathan Kline Institute (Rockland Sample) via the 1000 Functional Connectomes Project.

Behavioral Measures: Delis Kaplan Executive Function System; Wechsler Abbreviated Scale of

Intelligence; Impulsive Behavioral Scale; Adult Self Report (externalizing behavior).

Cortical Analysis: structural data were processed and analyzed using the Freesurfer 5.3.0 image analysis software suite.

Subcortical: anatomical imaging data were segmented into subcortical regions using FSL's FMRIB Integrated Registration and Segmentation Tool (FIRST).

Results

Results suggest: increased left hemisphere superior parietal thickness related to increased performance on the DKEFS and WASI. Also, decreased right hippocampal volume and shape changes were associated with increased scores on the UPPS Total and ASR. Age and intracranial volume were controlled for in all analyses.

Conclusions

These results suggest that increased parietal thickness is associated with increased EF, possibly indicating a common neural substrate between the two. Increased parietal thickness may suggest better functioning of the frontal-parietal attentional system. Furthermore, decreased right hippocampal volume and shape changes were associated with both increased UPPS and ASR, suggesting a common neural region of interest. Decreased hippocampal volume may indicate poorer reliance or retrieval of memory to guide decision making.

Disclosures: **K. Mattingly:** None. **L. Faul:** None. **B. Depue:** None.

Poster

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Program #/Poster #: 073.09/VV11

Topic: G.02. Motivation

Support: Valley Baptist Legacy Foundation Center for Brain Health Grant

Title: Mapping consumer cognition and emotions: A machine learning approach

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Abstract: Decision making is key to consumer behavior and is pervasive in ecological situations and thus has been studied by various disciplines, including economics, psychology, and marketing, as well as consumer neuroscience. Marketing studies focus on the behavior from three different perspectives, namely cognitive (consumers' cognitive decision-making process); experiential (consumers' emotions based on experience), and environmental (consumer as affected by others' behaviors and surrounding circumstances). However, marketing has traditionally used a survey, self-reported measurements, limiting conclusions regarding the role

and interactions of emotions and cognition in decision-making. We used Activation Likelihood Estimation (ALE) meta-analysis and functional magnetic resonance image (fMRI) data to compare the explanatory ability of each perspective to understand consumer decision-making. Two independent studies were performed: First we used ALE meta-analysis to identify which brain regions have been associated with consumers' behavior directed by cognition or specific emotions. We searched PubMed articles focused on emotions (happiness, sadness, anger, fear, and disgust) and cognitive behaviors (memory and language) to obtain MNI coordinates describing the activated brain regions. We then employed Multi-image Analysis GUI (Mango, <http://ric.uthscsa.edu/mango/>) to graph average brain regions based on the coordinates and evaluated consensus overlap. Second, we used a machine learning algorithm to draw a brain map of consumer decision-making based on the findings of the meta-analysis, on a Human Connectome Project dataset and to draw a brain map showing functional connectivity among brain regions activated for each behavior. Lastly, we analyzed the impact of personality profiles using NEO test results on the connectivity maps from HCP.

Disclosures: G.A. De Erausquin: None. D. Rew: None. M. Minor: None.

Poster

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Topic: G.02. Motivation

Support: CNPq Grant 311117/2016-3
CAPES

Title: Punishment sensitivity and implicit motivational behavior in people with food craving

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Abstract: The study of motivation is relevant for the eating behavior literature. Personality factors (e.g., reward and punishment sensitivity) and eating behavior constructs (e.g., food craving - FC) are commonly used to identify biases in the approach / avoidance motivation to food and food-related stimuli. Thus, novel behavioral measures of motivation can be combined with measures associated with overeating to find risk groups for obesity and eating disorders. Two studies were conducted to describe factors associated with motivation and overeating. In Study 1, demographic, psychological and personality (ie, reward and punishment sensitivity) components were used to predict the levels of FC in a non-clinical population of university

students (n = 208), ages between 18 and 30 years, with a BMI range between 16.90 and 45.31. In a linear regression to predict FC, two variables significantly contributed to the final model, explaining 24% of its variance: family history of obesity ($\beta=-0.14$, $p = .012$, 95% CI from -21.93 to -1.65) and BIS-Anxiety ($\beta=0.23$, $p <.001$, 95% from 2.06 to 6.14). In Study 2, selected participants of the first study were divided in High FC (n = 31, mean age: 21.29 years) and Low FC (n = 29, 22.31 years) and performed a novel version of the Approach-Avoidance Task with three conditions: approach (appetitive food x neutral), avoidance (aversive food x neutral), and conflict (appetitive food x aversive food). The High FC group had significantly higher scores of BIS-Anxiety, (U = 236, $p = .001$, $r = -0.41$) and BMI (U = 251, $p = .015$, $r = -0.32$) An interaction in the ANOVA 2x3 comparing groups and motivational conditions of the AAT revealed that the High FC group displayed a significantly higher avoidance towards the aversive stimuli compared to neutral stimuli (ie, aversive condition) and appetitive stimuli (ie, conflict condition) than the Low FC group (F (2, 104) = 3.24, $p = .043$, partial $\eta^2 = 0.059$). Neither of the groups presented a significant approach bias to appetitive stimuli. There were no correlations between scores in conditions and measures of personality. Data of both studies suggests a relationship between FC and punishment sensitivity. Also, participants with high FC showed greater reaction and avoidance bias to aversive stimuli compared to neutral and to appetitive stimuli. When controlling for personality factors associated with overeating behavior, future studies with behavioral measures can elucidate in which conditions food stimuli are more salient than other environmental features (e.g., aversive cues) to risk groups for obesity and eating disorders.

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Poster

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Topic: G.02. Motivation

Support: Thomas P Detre Fund at Yale University.

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NIH T32 MH018268

NIH

T32 MH019961

Title: Monetary incentives shape behavioral and neural precision of spatial working memory

Authors: *Y. CHO¹, C. H. SCHLEIFER¹, F. MOUJAES¹, M. STARC², L. JI¹, N. SANTAMAURO¹, B. ADKINSON¹, A. KOLOBARIC¹, M. FLYNN¹, J. KRISTAL¹, J. D.

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Abstract: Incentive representation confers a key influence on motivated, goal-directed behaviors. Yet, little is known about how incentives influence neurocognitive circuits in humans. Here we studied the effects of cued and non-cued monetary incentive presentation on spatial working memory (WM) performance using functional magnetic resonance imaging (fMRI). 33 healthy adults performed a spatial WM task that incorporated gain and loss monetary incentives. The sWM task incorporated eye tracking and captured continuous responses via a high-precision, scanner-compatible joystick. The possibility for monetary gain or loss was presented either as a cue prior to each spatial WM trial (cued), or as an initial context instruction across a block of WM trials (non-cued). Images were collected using multi-band sequences and parameters consistent with protocols from the Human Connectome Project (HCP). Pre-processing followed HCP pipelines, and permuted statistics were used for whole-brain analyses. WM precision improved when the possibility for monetary gain or loss was presented in a cued manner ($p < 0.001$, both), and in a non-cued manner ($p < 0.01$, both). The neutral, baseline spatial WM task engaged canonical frontal-parietal, motor and visual areas ($p < 0.05$, whole-brain corrected). We conjuncted this result with a whole-brain corrected map of cued incentive effects, which revealed signal modulation across parieto-occipital, motor, and anterior cingulate cortices during incentive conditions. A further conjunction of this map with a whole-brain corrected map of non-cued incentive effects showed a highly similar but attenuated pattern. We examined the relationship between trial-by-trial sWM precision (calculated as cue-probe angular deviation) and voxel-wise signal, which revealed a significant relationship between sWM precision and signal change in the inferior parietal sulcus, superior frontal sulcus and frontal eye fields. Critically, these precision-related signals were further modulated by incentive. Collectively, our results demonstrate that incentives improved sWM performance, and that distinct patterns of cortical modulation reflected the influence of cued and non-cued incentives on sWM. Furthermore, results highlight specific cortical areas where increased signal tracks trial-by-trial sWM precision. This study pinpoints neuro-behavioral incentive-cognition interactions in humans with translational potential to clinical conditions that may affect these computations.

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Poster

074. Emotion: Human Emotion I

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Program #/Poster #: 074.01/VV14

Topic: G.03. Emotion

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BBRF NARSAD Young Investigator Award to PRB

Title: Anterior cingulate glutamate and amygdalar activation in response to emotional stimuli, impact of personality traits

Authors: *P. R. BURGHARDT¹, A. S. NEFF², K. NOWAK¹, J. A. STANLEY³
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Abstract: The combination of fitness and psychological traits are thought to influence individual coping strategies. Neuroticism has been inversely associated with quality of life, while extroversion is associated with increased quality of life over time. Aerobic fitness has shown a protective benefit. The general relationship between aerobic fitness with trait personality, and the underlying neurobiology, in healthy individuals has not been well described.

Here we begin to investigate the relationship between fitness and neuroticism on the neurobiological response to emotional stimuli. Personality traits and cardiopulmonary fitness were measured in ten health individuals using the NEO Personality Inventory and maximal oxygen consumption (VO₂max), respectively. During a separate visit, in vivo proton functional magnetic resonance spectroscopy (¹H fMRS) was used to investigate the modulation of the neurotransmitter glutamate (Glu) in the anterior cingulate cortex (ACC) during an image appraisal task. Additionally, whole-brain functional activity during image appraisal was assessed using BOLD fMRI. During ¹H fMRS and fMRI, subjects assessed images from the Nencki Affective Picture System (NAPS) consisting of pictures ranked to have positive (E+), Negative (E-), or neutral (En) emotional valence.

Trait neuroticism was inversely associated with aerobic fitness. Preliminary analyses indicate that a positive association exists between VO₂max and the ACC Glu modulation in response to E+. No association was found between neuroticism and ACC Glu modulation response to any of the stimuli types. BOLD activation in the amygdala was associated with Neuroticism, but not Extroversion during appraisal of E-. Modulation of Glu in the ACC was negatively associated with BOLD activation in the Amygdala during viewing of E+, but not E-.

These preliminary results suggest increased aerobic fitness is associated with increased glutamatergic neurotransmission in the ACC of individuals during appraisal of pictures with a positive emotional valence. Further, the relationship between glutamatergic neurotransmission in

the ACC and amygdalar BOLD signal may be influenced by trait personality. These results will help inform treatment strategies for individuals with psychiatric disease.

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Poster

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Title: Trait conscientiousness correlates with the abundance of major bacterial phyla in the human gut

Authors: *A. NEFF¹, K. NOWAK², K. CHAPPELLE², P. BURGHARDT²
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Abstract: Background: Growing evidence supports the existence of a bidirectional communication between the gut microbiome and brain function. But the range of human cognition and behavior relating to the gut microbiome is still unknown. To further explore which aspects of human psychology and behavior correlate with which aspects of the gut microbiome, we measured personality and physical fitness and compared them with the composition of the gut microbiome. Methods: From a sample of 15 subjects, fecal samples were collected, personality was measured with the NEO-PI, and measures of physical fitness were evaluated including resting energy expenditure and maximal oxygen consumption were measured using indirect calorimetry. All correlations were evaluated with Spearman's rho and corrected for multiple comparisons with FDR. Results: At the bacterial phylum level, conscientiousness correlated with lower levels of Bacteroidetes ($p=0.001$), and increased Firmicutes ($p=0.006$). At the level of individual genera, we found a negative correlation between agreeableness and a member of the Ruminococcaceae family ($p<0.001$). There were no significant correlations with fitness variables that survived FDR correction. Conclusions: These data indicate a connection between the composition of the gut microbiome and trait aspects of human psychology. Future work will examine if these relationships are related to behavioral endpoints related to health and wellness.

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Poster

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Topic: G.03. Emotion

Title: An automated emotion extractor of scenes that mimics the canonical human viewer

Authors: *B. R. SHETH¹, S. AMBATI²

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Abstract: Emotions often drive us and our behaviors. Certain scenes, movies, stories, commercials invoke a strong visceral, emotional reaction in our brains. An ability to reliably and automatically estimate the degree and kind of emotion aroused has application in social media, business analytics, human interaction etc., i.e. any enterprise in which human behavior is an integral component. Two dimensions of emotion are key in this regard: arousal value, or the extent to which a scene excites or calms the canonical viewer, and its valence, i.e. the extent to which the scene is pleasant or unpleasant. Past attempts to automate emotion detection in images have failed for a variety of reasons, e.g. lack of images independently evaluated for emotional content, limited generality of approach, use of low-level features like color, texture etc. Our novel, integrated approach overcomes said limitations: For each image of IAPS and NAPS - standardized databases of images whose emotional content has been independently measured using human raters -, it weights several high-level semantic features, which were extracted by a deep learning network, and sums the weighted contributions to arrive at numerical values for arousal and valence. The model has two parts: a front-end consisting of a bank of classifiers, where each classifier evaluates the probability of a particular semantic category (e.g. a human) in the image; a back-end regressor that takes the front-end outputs and weights the contribution of each semantic category to generate numerical values for valence and arousal. The front-end classifiers were extensions of the deep learning network Inception_v3. Training images were obtained from google images, so the model never saw IAPS or NAPS images during training. The numerical values of valence and arousal output by the model were linearly correlated significantly ($p \ll 0.0001$ for both arousal and valence) with manual ratings, and were discretized to one of two classes for valence (high/low) and three classes for arousal (high/medium/low). Overall system performance was evaluated by comparing the model class with ground truth, i.e. the class obtained from discretizing the mean ratings provided by human raters in the IAPS and NAPS studies. Our best performing model demonstrated test accuracy of 98.0% on valence (chance = 50%) and 95.0% on arousal classification (chance = 33%) across IAPS+NAPS (n=2202 images combined). We further tested the model on GAPED - a third externally validated set of images (n=730) that were never shown or used to train the model - and

it, again, exhibited high levels of accuracy: 96.4% on valence and 92.5% on arousal classification.

Disclosures: **B.R. Sheth:** None. **S. Ambati:** None.

Poster

074. Emotion: Human Emotion I

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Topic: G.03. Emotion

Support: DFG Emmy-Noether WU 758/1-1

Title: Attributing success to oneself versus another: Dissociating neural correlates of pride and gratitude

Authors: ***K. DING**¹, D. ANGGRAIN², K. WUNDERLICH¹

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Abstract: Gratitude and pride are both feelings related to accomplishment, whereby the pride attributes success to oneself and gratitude to another. Gratitude and pride are vital to the function of a society, allowing one to create interpersonal relationships and build self-confidence. Despite growing interest in the neural underpinnings of positive emotions and subjective feelings, we know very little about how these emotions are represented in the brain and computationally updated over time by new experience.

We developed a novel behavioral task based on the gameshow 'Who Wants to be a Millionaire', which we used together with functional MRI, and computational modeling. We investigated which brain regions are involved in representing gratitude and pride, how the human brain keeps track of these emotions over time and how it updates them when new information is available. We found that gratitude was more associated with neural activities in the bilateral temporoparietal junction (TPJ), which has previously been implicated in theory of mind. In contrast, pride was more associated with neural activities in the caudate nucleus, which is part of the reward system, and hippocampus. Importantly, when we look for neural activity parametrically modulated with the reported magnitude of gratitude feelings we found correlations mainly in the motor cortex (precentral gyrus), reward system (ventral striatum, putamen) and theory of mind network (temporal pole). In contrast, neural activity pertaining to the strength of the feeling of pride was found in the bilateral putamen. Finally, activity in ventromedial prefrontal cortex (vmPFC) was related to an emotional prediction error signal, suggesting that this region might be involved in the process of updating our level of gratitude and pride feelings.

Our findings delineate the computational mechanisms and neural circuitry for positive emotions that accompany the attribution of getting reward whether it is due to one's own effort or the help of others.

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Poster

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Title: Dynamical integration and segregation of emotion-related brain circuitry linking to physiological arousal in humans

Authors: *F. TAO^{1,2}, L. WU^{1,2}, Z. CUI³, L. HAO^{1,2}, Y. ZHU^{1,2}, S. QIN^{1,2}

¹State Key Lab. of Cognitive Neurosci. and Learning, ²IDG/McGovern Inst. for Brain Res., Beijing Normal Univ., Beijing, China; ³Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The brain is an open and highly sophisticated system, consisting of a complex network of brain regions that engage and disengage constantly with each other to support rapid adaption in ever-changing environment for survival. Understanding the dynamic nature of brain functional networks is crucial to delineate the neurophysiological bases underlying human cognition and emotion in healthy and psychiatric conditions. Although dynamic profiles of large-scale brain functional networks have been widely investigated during resting state and learning activities, little is known about dynamic states of emotion-related brain circuitry and their relation to spontaneous fluctuation of physiological signals. Here we analyzed three independent datasets to quantify dynamic states of functional connectivity of emotion-related brain circuitry implementing sliding-window and K-means methods. First, analysis of resting-state fMRI data from 42 adults (21-24 years old) revealed two clearly dissociable states of amygdala-subregional functional connectivity with widespread regions including subcortical structures, cerebellum, uni- and polymodal association cortex, limbic and paralimbic structures, and prefrontal cortex, with one segregated state showing generally stronger BLA-based functional connectivity with other widespread neocortical regions than CMA-based connectivity, and the other integrated

state showing considerable overlapping between BLA- and CMA-based connectivity networks. The segregated state occupied greater proportion of total time (mean \pm SEM = 60.01 \pm 0.76%) across participants than integrated state (mean \pm SEM = 39.99 \pm 0.76%). Critically, these two states were reproducibly identified in a second independent cohort of 41 age-matched healthy adults and a third independent cohort with concurrent skin conductance recording in 21 age-matched healthy adults. Further analysis of skin conductance level (SCL) data revealed a significant difference between two different states, with higher SCL in the integrated than segregated state. This result indicates a correspondence of emotion-related brain circuitry states with fluctuations of physiological arousal. Our findings suggest that a potential neurobiological mechanism underlying dynamical integration and segregation within emotion-related brain functional circuitry and it links to spontaneous fluctuations of physiological arousal in humans.

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Poster

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Title: Adversity-gastrointestinal-anxiety associations across human development

Authors: *B. L. CALLAGHAN¹, A. FIELDS², D. G. GEE⁴, L. J. GABARD-DURNAM⁵, C. CALDERA⁶, K. HUMPHREYS⁷, B. GOFF⁸, J. S. FLANNERY⁹, E. H. TELZER¹⁰, M. SHAPIRO⁶, N. L. TOTTENHAM³

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Abstract: Gastrointestinal and mental disorders are highly comorbid and share environmental risk factors. Specifically early adversity is strongly associated with the onset of gastrointestinal and mental illnesses in humans, and within rodent models, a causal relationship has been

established. Interactions between bacteria that live within the gastrointestinal system, the microbiome, and the brain might underlie adversity-gastrointestinal-anxiety associations, but the relationships between these myriad factors are not frequently investigated in developmental populations. We have utilized data from a population of 344 children and adolescents (3-18 years old) that were raised with their biological parents or were exposed to adverse caregiving experiences during infancy (i.e., institutional or foster care followed by international adoption) to explore adversity-gastrointestinal-anxiety associations. We demonstrated that previous adverse care experiences were associated with an increased incidence of gastrointestinal symptoms in children and adolescents. Gastrointestinal symptoms were also associated with concurrent and future anxiety (measured across 5 years) and those gastrointestinal symptoms mediated the adversity-anxiety association. In a sub-sample of children that provided both stool samples and functional MRI of the brain, adversity was associated with changes in diversity (both alpha and beta) of microbial communities, and bacteria (adversity-associated and adversity-independent) was correlated with prefrontal cortex activation to emotional faces. The implications of these data for supporting child and adolescent mental health are discussed.

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Poster

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Topic: G.03. Emotion

Support: NSF SMA 1041755

Title: Perceiving emotional sounds(MAARI): Individual differences, prior learning and context

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Abstract: For over half a century, research on emotional information perception and the neural processes underlying human cognition and behavior has primarily focused on visual perception. However more recently, increasing research on auditory emotional information processing has helped contribute valuable new insights into understanding the role emotion plays in successfully negotiating the world.

We investigated the interactions between auditory emotion perception and other factors

including physical condition, personality traits, political beliefs, relationships, bilingualism, and birth order. First we developed MAARI, the Multidimensional Auditory Affect Ratings Inventory (Society for Neuroscience 2013), a set of 650 non-verbal emotive vocalizations, standardized for length, amplitude and onset amplitude. Then 822 participants (F=609, M=213) performed 1072 ratings of MAARI vocalizations on three of the following five dimensions: valence, arousal, dominance, authenticity and personal impact. Participants then took a battery of psychological tests (including PANAS-X, Basic Emotional Empathy Scale, Big 5 Personality Scale, Toronto Alexithymia Scale, Narcissism scale, Jungian Type, and Beck Depression Inventory), also providing extensive demographic information on themselves and their caregivers.

There were significant interactions between factors commonly considered “non-emotive” such as physical condition, Big Five Personality traits, political beliefs, birth order, and the ratings the individuals assigned to the MAARI emotive vocalizations. These interactions indicate auditory emotion perception both influences and is influenced by “non-emotive” factors, both internal (intrinsic and learned) and external (contextual) to the individuals who heard and rated MAARI non-verbal emotional vocalizations.

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Poster

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Topic: G.03. Emotion

Support: CONACYT 1840

Title: Differences in the evaluation of affective images between young and middle adults in the presence of affective disorders

Authors: ***E. ACOSTA**¹, **X. CORTIJO-PALACIOS**², **B. BERNAL-MORALES**², **A. ESCALANTE-VARELA**³, **A. SANCHEZ-HIDALGO**³, **M. CADENA-BARAJAS**⁴, **T. CIBRIAN-LLANDERAL**⁵

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Abstract: Introduction: The International Affective Picture System (IAPS) was developed to provide a set of standardized stimuli for experimental investigations of emotional processes.

Objective: Identify the differences in the assessment of a block of images of IAPS when applied to young and middle-aged adults in the presence of affective disorders.

Design and Methods: An observational, cross-sectional and descriptive study was carried out with a sample of 151 female and male participants. Two groups of volunteers, one consisting of 83 young adults and the second integrated for 68 middle-age individuals were formed. The participants were evaluated through the Beck Anxiety and Depression Inventory and the Toronto Alexithymia Test to assess the presence and severity of affective disorders. The emotional evaluation was carried out with a block of 60 images from the IAPS and was evaluated using the Self-Assessment Manikin (SAM) pictographic scale.

Results: With the use of descriptive statistics and the association between variables with the Wilcoxon Rank-sum Test ($P < 0.05$) and R statistical software, significant differences were found in 61.6% of the images evaluated between YA and MA. In the sample obtained YA the mean age was 20.73, 30% presented anxiety, 26% depression and 49% alexithymia. In the MA group, the mean age was 51.45, 8% presented anxiety, 26% depression and 21% alexithymia. In the presence of affective disorders were found statistically significant differences only in the 3% of the images evaluated for the MA group and 5% of the YA group.

Conclusion: Results have shown that the processing of the emotional contents is different between YA and MA, which suggest that human response to affective pictures depends on the stage of development and cognitive abilities of the individual. The presence of affective disorders in both groups of the population stands out, but this condition does not affect the emotional discrimination.

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Poster

074. Emotion: Human Emotion I

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Topic: G.03. Emotion

Support: Build Poder

Title: Differences in late positive potential in emotional information processing among individuals with alexithymia

Authors: *D. A. BANUELOS, K. JOHNS, S.-M. KANG
California State Univ. Northridge, Northridge, CA

Abstract: Few studies have explored how individuals with alexithymia process emotional information using the Electroencephalogram (EEG). Pollatos and Gramann's study (2011) demonstrated that individuals with high degrees of alexithymia (HDA) show an early processing deficit compared to individuals with low degrees of alexithymia (LDA) by focusing on P100 and P300 peaks. However, their study did not explore differences in the Late Positive Potential (LPP). A literature review has shown that emotion stimuli elicit a positive brain potential around 250ms after emotional stimuli are presented (Hajcak, Moser, & Simons, 2006; Hajcak & Nieuwenhuis, 2006). It was speculated that this elevated positive brain potential may imply the sustained attention to emotion stimuli (Hajcak & Olvet, 2008). One interesting question is whether there would be significant differences in the level of the LPP between individual with HDA and LDA. It was hypothesized that the group difference would be pronounced in processing negative emotions than positive or neutral emotions.

From a pool of 592 college students who took the Toronto Alexithymia Scale (Bagby et al., 1994), the top or the bottom 10% of the participants selected based upon their score were invited to participate. Of the 23 participants, usable data from 12 participants (7 high and 5 low) were included in the final analyses. In an individual session, a 64-channel cap was applied on a participant's head following the 10/20 system. The electrooculogram generated from blinks and eye movements was recorded from 4 facial electrodes. The participant was asked to watch images taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) presented on a computer screen, while the EEG are continuously recorded. A total 120 pictures (40 positive, 40 negative, and 40 neutral photos) were presented by emotion and in a random order.

The results of the current study revealed that the mean LPP for the negative emotion between high and low alexithymia conditions were significantly different from each other within the time window of 400ms to 2000ms, $F(1,10) = 7.59, p = .020$. The average LPP of the HDA group ($M = .3394, SD = 1.6792$) was significantly higher than that of the LDA group ($M = -2.4046, SD = 1.7331$). However, this significant group difference completely disappeared in the time window of 2000 to 3000ms, $F(1,10) = .00, p = .991$.

No significant group differences were found in the positive or neutral emotion conditions across two time windows. The significance and implications of the heightened attention to negative emotion by individuals with HDA were discussed in terms of their over-regulated experiences of negative emotion.

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Poster

074. Emotion: Human Emotion I

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Topic: G.03. Emotion

Support: NIMH Grant R15MH1109051

Title: Error monitoring in anxious individuals: Relationship between electrocortical responses and neuroanatomical variability

Authors: ***J. A. ANDRZEJEWSKI**, L. FANG, R. J. SYLVIAN, J. M. CARLSON
Northern Michigan Univ., Marquette, MI

Abstract: The electrocortical activity resulting from an individual committing an error in a behavioral task is readily indexed by the error-related negativity (ERN)—a response-locked event-related potential (ERP) featuring an increase in negative amplitude 0-100 ms after an erroneous response that is maximal at frontocentral electrodes. It is known that anxiety is accompanied by ERN increased sensitivity to errors and increased ERN amplitude. However, the relationship between electrocortical activity resulting from error monitoring and the underlying neuroanatomical structures in anxious individuals is less established. To address this question, participants who self-reported high levels of trait anxiety completed two neuroimaging procedures. One procedure involved the acquisition of T₁-weighted images from a MRI. The MRI images were then subsequently segmented into gray matter, white matter, and cerebral spinal fluid; voxel-based morphometry (VBM) was used for analysis. The other procedure had the participant perform the Eriksen Flanker Task while connected to a 64 channel 10-20 system EEG in order to measure ERN amplitudes. The Eriksen Flanker Task consists of both incongruent (e.g. < > < <) and congruent (e.g. < < < <) stimulus presentation. The participant was tasked with indicating, via stimulus response box, the direction of the center arrow. The rapid presentation of the stimuli and the subtle differences in stimulus presentation has the participants make enough errors to engage in error monitoring, which is reflected by ERN ERP electrocortical activity. The ERP results from this study indicate that erroneous responses resulted in significantly more negative amplitudes when compared to correct responses; this response was maximally seen between 0-100 ms at the electrode Cz. In order to investigate the relationship between ERN amplitude and structural variability, an ERN amplitude difference was first calculated by subtracting incorrect response amplitudes from correct response amplitudes. A multiple linear regression was performed with the ERP and VBM data: intracranial volume was considered a covariate and ERN amplitude difference was treated as a predictor of gray matter volume. A significant relationship between an increase in ERN difference amplitudes and gray matter volume in the prefrontal cortex was found. These results suggest that structural variability is related to the variability in the ERN amplitudes in individuals with high trait anxiety.

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Poster

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Program #/Poster #: 074.11/WW2

Topic: G.03. Emotion

Title: Greater intensity of subjective emotional experience with increasing magnitude of electrical stimulation in human cingulate, insular, and orbitofrontal cortices

Authors: *J. YIH, D. E. BEAM, K. C. R. FOX, J. PARVIZI
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Abstract: Electrical brain stimulation in awake neurosurgical patients often elicits emotion-related responses, including diverse effects on autonomic activity and emotional state, as well as the elicitation of sensory effects, such as valenced smells and tastes. To date, it remains to be determined how the parameters of electrical stimulation might relate to the perceived intensity of these elicited emotional effects. Our research in the visual domain has clearly suggested that changes in the magnitude of electrical charge can modulate the size of visual field where phosphenes are perceived (Winawer & Parvizi, 2016). In the current study, we extend our previous findings to the emotional domain by clarifying the relationship between stimulation parameters and subjective emotional experience. In 17 patients (7 female; $M = 40$ years old, $SD = 13$ years) implanted with depth (50%) or subdural (38%) electrodes, or a mix of both (13%), we stimulated 150 electrodes in cingulate, insular, and orbitofrontal cortices. Occasional sham stimulations were also randomly delivered to control for demand characteristics. We identified 76 electrode sites (32% cingulate, 21% insular, and 47% orbitofrontal) in which stimulation elicited subjective emotional responses. Focusing on these electrodes that elicited responses during stimulation, when there was a change in stimulation magnitude (amplitude or frequency), we observed changes in the reported intensity of subjective emotional experience for the majority of these electrodes. Changes in the amplitude or frequency were directly correlated with changes in subjective emotional experiences in the domains of olfaction/gustation, autonomic/bodily responding, both, or neither (i.e., miscellaneous effects devoid of sensory or bodily changes). Our findings demonstrate that changing the magnitude of electrical stimulation to human cingulate, insular, and orbitofrontal cortices typically changes the subjective intensity of emotional experience. As implanted electroceutical interventions are increasingly employed to treat neuropsychiatric disorders, these findings have important implications for clinicians attempting to modulate emotional experience with intracranial electrical stimulation.

Disclosures: J. Yih: None. D.E. Beam: None. K.C.R. Fox: None. J. Parvizi: None.

Poster

074. Emotion: Human Emotion I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 074.12/WW3

Topic: G.03. Emotion

Support: Ministry of Education (MOE) Academic Research Fund (AcRF) Tier 1, Singapore
College of Humanities, Arts, and Social Sciences (CoHASS) Incentive Scheme,
Nanyang Technological University (NTU)
NTU Research Scholarship (RSS)

Title: Neural correlates of facial emotion perception with alexithymia and autistic traits

Authors: *H. XU, K. SOU, E. BURNS
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Abstract: Alexithymia is a personality construct characterized by an inability to describe or identify feelings. It is commonly comorbid with autism and has been identified as the underlying cause of emotion recognition deficits in the autistic population. While numerous studies utilizing fMRI have established the neural regions that display abnormal activity during emotion processing in individuals high in alexithymia, the stage of processing at which the deficits begin to emerge remains unclear. In the present EEG study, we aimed to identify the time-course of atypical facial emotion recognition in highly alexithymic individuals, while also controlling for their autistic traits.

Twenty-two subjects (11 with high alexithymia traits) completed a facial expression recognition task while their brain activity was recorded via EEG. In the task, either a neutral face, angry face or a happy face was shown on the screen and subjects were asked to identify the emotion of the presented face. Two sets of self-report scales measuring alexithymia (TAS-20) and autistic traits (AQ-50) were administered.

Preliminary results revealed an early frontal N2 component in high alexithymia subjects when perceiving angry faces. Further analysis showed that the frontal N2 latency was significantly correlated with the subjects' TAS-20 score and its subscales, even after controlling for autistic traits. On the other hand, the right-lateralized index of the N170 was significantly correlated with AQ-50 score, and remained marginally significant after controlling for TAS-20 score.

We conclude that the abnormality in facial emotion recognition in high alexithymia individuals occurs as early as 240ms post-stimulus onset in the frontal neural regions. This supports the frontal region hypothesis of alexithymia. In contrast, autistic traits appear to predict the lateralization of emotional face perception, which may be related to holistic vs. featural processing.

Disclosures: H. Xu: None. K. Sou: None. E. Burns: None.

Poster

074. Emotion: Human Emotion I

Location: SDCC Halls B-H

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Program #/Poster #: 074.13/WW4

Topic: G.03. Emotion

Support: National Research Foundation of Korea (NRF) #2015-R1A2A2A04006136

Title: Exploring the impact of emotional labor on social attention and brain connectivity patterns

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Abstract: Emotional labor refers to a process in which workers are expected to regulate their feelings and emotional expression during interactions with clients. It has been implicated that a high level of emotional demands in work can lead to burnout and self-alienation. Although an increasing number of workers suffer from negative effects of emotional labor, only a few studies have investigated the impact of emotional labor in neural level. The present study thereby aims to discriminate neural activities of emotional laborers and non-emotional laborers when encountering emotional conflicts. Eighteen emotional laborers and twenty healthy controls were recruited and underwent functional magnetic resonance imaging (fMRI). Two conditions were set in the experimental task: congruent and incongruent conditions. In the congruent condition, participants viewed two neutral facial expressions. In contrast, one neutral and one negative facial stimulus were presented in the incongruent condition. First, we used general linear modeling (GLM) method to compare brain activations across conditions and groups. GLM results showed heightened activations of the insula and middle temporal gyrus, and decreased activations of the amygdala and hippocampus in emotional laborers when viewing conflicted emotions. Next, functional connectivity multivariate pattern analysis (fcMVPA) using support vector machine algorithm was conducted to discriminate brain connectivity patterns of two groups. fcMVPA classified emotional laborers and controls with an accuracy of 92.86% using 56 features in incongruent trials. The insula and prefrontal cortex showed the highest degree centrality values in performing the classification. In congruent trials, however, two groups were classified with a decreased accuracy of 85.71%. Also, a larger set of 766 features were required to elicit the performance, which suggests decreased network efficiency in classifying two groups. These findings suggest that functional connectivity patterns centering the insula differ in emotional laborers and non-emotional laborers especially when encountering incongruent social stimuli. Furthermore, it has been implicated from previous studies that repeated exposure to aversive stimuli results in behavioral habituation along with decreased amygdala activation and

increased insula activation. Emotional laborers showed the same pattern of altered activations both in the amygdala and insula, which suggests that due to persistent exposure to stress and emotive dissonance, they may have been habituated, rather than biasedly attentive, to negative social stimuli.

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Poster

074. Emotion: Human Emotion I

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Topic: G.03. Emotion

Support: University of Florida Clinical and Translational Science pilot award (NIH/NCATS; UL1 TR000064)
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Scientific Research Network on Decision Neuroscience and Aging
Mentorship/Collaboration Award (NIH/NIA, R24-AG054355)

Title: Oxytocin modulation of amygdala connectivity varies by age and facial emotion

Authors: ***M. HORTA**¹, **M. ZIAEI**³, **R. N. SPRENG**⁴, **H. FISCHER**⁵, **D. FEIFEL**^{6,7}, **N. C. EBNER**^{1,2}

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Abstract: Accurately reading facial emotions is a crucial skill for successful social interactions across the lifespan. Aging, however, is associated with increased difficulty in facial emotion identification. The underlying neural mechanisms of this age-related deficit are still largely unknown but could be associated with age-related change in network communication among brain regions involved in face and emotion processing. Growing evidence suggests that oxytocin (OT) modulates the ability to identify facial emotions but these social-cognitive effects of the neuropeptide are understudied in aging. To determine the effects of OT on behavior and brain networks relating to dynamic facial emotion identification, 46 young ($M = 22.5$ years, $SD = 3.1$,

18-31 years, 47.8% female) and 48 older ($M = 71.1$ years, $SD = 5.2$, 63-81 years, 56.3% female) participants self-administered intranasal OT (24 IU) or a placebo (P) in a between-subject, randomized, double-blind procedure. While undergoing fMRI scanning, participants viewed neutral faces that morphed into emotional expressions (sad, angry, fearful, happy) and indicated which emotion was displayed. In line with the literature on static facial emotions, older compared to young participants were slower and less accurate in identifying all, but particularly negative, dynamic emotions. There was no behavioral treatment (OT vs. P) effect on emotion identification. Exploratory seed partial least squares (PLS) analysis showed that functional connectivity of the left amygdala (MNI = -28, -6, -12) to the rest of the brain varied by age and facial emotion. Amygdala connectivity was increased for young participants in the OT compared to the P group in response to fearful faces and for young compared to older participants in the OT group in response to sad faces (Latent Variable 1: 52.58% cross-block covariance, $p = 0.002$). Regions within this network included the thalamus, temporal gyrus, substantia nigra, hippocampus, insula, post cingulate, inferior parietal lobule, and medial frontal gyrus across both age groups. Furthermore, amygdala connectivity in older adults varied by treatment group in response to happy, sad, and angry faces (Latent Variable 2: 7.92% cross-block covariance, $p = 0.002$). While older adults in the OT group recruited a large-scale network, including the ventromedial prefrontal cortex and anterior cingulate, older adults in the P group recruited a smaller network, including the fusiform gyrus and insula. These findings suggest that age-related differences persist for dynamic (compared to static) facial emotion identification and that OT modulates amygdala connectivity as a function of age and facial emotion.

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Poster

074. Emotion: Human Emotion I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 074.15/WW6

Topic: G.03. Emotion

Title: Neurite density imaging in amygdala nuclei reveals interindividual differences in neuroticism

Authors: *C. T. SCHLÜTER, C. FRAENZ, P. FRIEDRICH, O. GUNTURKUN, E. GENC
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Abstract: Neuroticism is known to have significant health implications. Although previous research confirms that individual differences in the amygdala function are associated with individual differences in the degree of neuroticism, the impact of individual differences in the structure of the amygdala remains unclear. Some post-mortem studies on mood disorders, which

are strongly associated with neuroticism, indicate that differences in the microstructure of the amygdala might lead to the adverse emotionality that can be seen in both the respective disorder and neuroticism. However, up to now, no one has studied whether individual differences in neuroticism are associated with differences in the microstructural architecture of the amygdala. Here we present the first study using NODDI to examine the in vivo microstructural architecture of the human amygdala to shed light on the possible neuroanatomical underpinnings of neuroticism. We acquired brain images from 221 healthy participants using advanced multi-shell diffusion tensor imaging. Since the amygdala is not a uniform tissue, but a cluster of sub-nuclei that differ in both structure and function, we used a high-resolution structural image to automatically segment the amygdala into eight different sub-nuclei. Further, we acquired neuroticism using the NEO-PIR. Since neuroticism, as measured by the NEO-PIR, is heterogeneous construct including six, partly opposing, facets, our analysis not only considered the main scale but also included the facets of neuroticism. Finally, we associated neuroticism and its facets with the microstructure, measured as dendritic density and arborization, of the amygdala sub-nuclei. Statistical analyses revealed that solely the dendritic density in the lateral nucleus of the amygdala was significantly associated with the individual's shaping in depression, one of the six neuroticism facets ($r = -.224$, $p < .000$). These effects remained stable after controlling for the effects of age and sex. The lateral nucleus is considered to be the sensory relay of the amygdala, evaluating and transmitting incoming information. A lower neurite density in this nucleus, as detected in individuals with higher neuroticism, might impair this function. Thus, potentially harmless sensory information could be misvalued as threatening and thus lead to an increase in general amygdala responsivity. This altered amygdala responsivity is not only reported in studies on the functional correlates of neuroticism it is also associated with mood disorders like depression. Thus, our study provides a crucial contribution to the mechanisms behind neuroticism and related mood disorders.

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Poster

074. Emotion: Human Emotion I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 074.16/WW7

Topic: G.03. Emotion

Support: KAKENHI, No. 15K00210

KAKENHI for Innovative Areas, No.25119006

Title: Odor induced autobiographical memory associated with slow breathing and medial prefrontal activity: fMRI study

Authors: *Y. MASAOKA¹, K. WATANABE¹, M. KAWAMURA², M. YOSHIDA³, N. KOIWA⁴, A. YOSHIKAWA⁵, S. KUBOTA¹, M. IDA⁶, K. ONO², M. IZUMIZAKI¹
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Abstract: Autobiographical odor memory (AM odor) accompanied by a sense of realism of a specific memory elicits strong emotions. AM odor differs from memory triggered by other sensory modalities, possibly because olfaction involves a unique sensory process. Here, we examined the orbitofrontal cortex (OFC), using functional magnetic resonance imaging (fMRI) to determine which OFC subregions are related to AM odor. Both AM odor and a control odor successively increased subjective ratings of comfortableness and pleasantness. Importantly, AM-odor also increased arousal levels and the vividness of memories, and was associated with a deep and slow breathing pattern. fMRI analysis indicated robust activation in the left posterior OFC (POFC). Connectivity between the POFC and whole brain regions was estimated using psychophysiological interaction analysis (PPI). We detected several trends in connectivity between left POFC and bilateral precuneus, bilateral rostral dorsal anterior cingulate cortex (rdACC), and left parahippocampus, which will be useful for targeting our hypotheses for future investigations. The slow breathing observed in AM-odor was correlated with rdACC activation. Odor associated with emotionally significant autobiographical memories was accompanied by slow and deep breathing, possibly involving rdACC processing.

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Poster

074. Emotion: Human Emotion I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 074.17/WW8

Topic: G.03. Emotion

Title: Chronic mild traumatic brain injury, napping, and emotional reactivity

Authors: *L. KURDZIEL, E. MAIER, G. JEWULA, A. CORMIER, R. SPINNEY
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Abstract: In 2003, the Centers for Disease Control and Prevention reported that mild traumatic brain injury (mTBI) is a “silent epidemic” due to the large number of mTBIs occurring yearly. Despite strong evidence linking emotional behavioral changes to mTBIs, more research is

needed examining physiological mechanisms that might explain this relationship. One possible mediating factor between emotional reactivity and mTBIs is sleep (Mantua, Henry, Garskovas, & Spencer, 2017). Sleep has been shown to be significantly altered in individuals with a mTBI (Mantua, Mahan, Henry, & Spencer, 2015). Sleep quality is also strongly linked with emotional stability and emotional memory (Baran, Pace-Schott, Ericson, & Spencer, 2012). The aims of this study were to determine whether individuals who have had a mTBI (over 1 year ago) show differences in performance on an emotional reactivity task, and show differences in sleep physiology across a nap compared to controls. Participants were 18 college-aged students (11 female; mTBI group: n=6; nap group: n=9). Participants were equipped with a 14-electrode polysomnography montage for both the nap and wake conditions. Following a nap, or an equivalent bout of sleep, participants completed an emotional Go/No-Go task in which participants observed facial expressions (neutral, fearful, happy) on a computer screen and were asked to respond when a particular emotional valence was presented, and withhold a response when a different valence was presented. There was a significant main effect of emotion on reaction time ($F(2, 13)=13.772, p = 0.001$). Participants were slowest to respond to the neutral images. There was a trending interaction between emotion and group on accuracy ($F(2,28)=2.88, p = 0.073$) such that the mTBI group was slightly less accurate at responding to the emotional (fearful and happy) stimuli compared to the control group and compared to neutrals. While there were no significant group differences in nap physiology, there were significant correlations between neutral RT and the percentage of the nap spent in nonREM2 ($r=0.805, p=0.016$) and nREM3 ($r=-0.793, p=0.019$). While these results are preliminary, they support that both napping and mTBIs may impact emotional reactivity.

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Poster

074. Emotion: Human Emotion I

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Program #/Poster #: 074.18/WW9

Topic: G.03. Emotion

Support: Melbourne Research Scholarship

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Title: The effects of high-dosage combination mental and physical training intervention on indices of stress and its emotion regulation, cardiorespiratory, and neurobiological mechanisms: A pilot study

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Abstract: Introduction: Evidence for interventions involving combined mental and physical training is showing promise for reducing psychosocial stress in clinical and nonclinical populations. The purpose of this pilot was to examine a high-dosage combination intervention involving mindfulness meditation and aerobic exercise training and its theoretical mechanisms to guide future fully-powered research. We focus on changes in use of emotion regulation strategies, improvements in cardiorespiratory fitness, and functional and structural adaptations of the brain. **Methods:** 17 healthy participants (males = 8; age: $M = 22.88$ years) were subjected to 16 weeks of combination training. The aerobic component comprised half-marathon training conducted three days/week, while the mindfulness component comprised daily formal meditation and weekly group psychoeducation. Self-report indices were assessed through questionnaires. Cardiorespiratory fitness was assessed through incremental exercise testing. Functional plasticity of focused-attention meditation was assessed through fMRI in a blocked design. Structural plasticity was assessed using VBM analysis. **Results:** The intervention yielded significant reductions in stress, repetitive negative thinking, and improvements in use of cognitive reappraisal. There was no change in VO_{2max} , but significant improvements in submaximal aerobic capacity. During focused-attention meditation, there were significant BOLD changes in regions associated with inhibitory control and selective attention (dorsal anterior cingulate) and introspective awareness (bilateral insula). There was a trend-level increase in hippocampal grey matter volume. **Conclusion:** These results provide preliminary support for high-dosage combination training for reducing stress. Potential emotion regulation, cardiovascular, and functional and structural mechanisms were identified. Effect size estimates derived from this study will allow for efficient sample size determination to assess these mechanisms in full-scale research.

Disclosures: P. Molenberghs: None.

Poster

074. Emotion: Human Emotion I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 074.19/WW10

Topic: G.03. Emotion

Support: NIMH DIRP

Title: Exploring the facial feedback hypothesis in Moebius syndrome

Authors: ***J. JORDAN**¹, S. LOKEY², C. I. BAKER³, L. G. UNGERLEIDER⁵, S. JAPEE⁴
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³Lab. Brain and Cognition, ⁴NIH, Bethesda, MD; ⁵Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The facial feedback hypothesis states that feedback from skeletal muscles of the face can alter the experience of an emotion. Therefore, individuals who cannot move their facial muscles, such as in Moebius Syndrome (MoS), may have difficulty experiencing and identifying emotion. MoS is a rare congenital neurological disorder, characterized by abnormality of the VIth and VIIth cranial nerves, resulting in paralysis of the face and lack of skeletal muscle feedback. Although several studies have examined the ability of MoS individuals to recognize and label emotions, findings have been mixed and it is unclear whether MoS results in deficits in emotion processing. To investigate this, we used an emotion detection task, a feature-detection control task and an emotion labeling task to assess emotion processing in MoS. For the emotion detection task, individuals with MoS and healthy controls were shown morphs of neutral to fearful, and neutral to happy faces. Subjects indicated whether they thought the face was neutral, fearful, or happy with a button press. A one-up three down staircase procedure was used to determine each participant's threshold for 79% accuracy. The same stimuli and staircase procedure were used in a feature-detection control task, but with instructions to indicate whether the mouth was open or closed. For the emotion labeling task, participants were shown images of 7 emotions (happy, sad, anger, disgust, fear, surprise, neutral) and were instructed to label the emotions, with 9 options corresponding to the 7 emotions, and "other" and "don't know" as additional choices. Results demonstrated that, compared to healthy controls, individuals with MoS showed a deficit in detecting fearful and happy faces, while performing similar to controls on the feature-detection control task. However, MoS individuals were no worse than controls on the labeling task. Taken together, these results indicate that facial paralysis in MoS and the associated lack of facial muscle feedback may impair emotion perception, providing support for the facial feedback hypothesis. In order to investigate the neurocircuitry underlying emotion processing in MoS, we used resting state functional MRI to measure the connectivity between face-selective regions including FFA, pSTS and amygdala. Our preliminary data indicate reduced pSTS-amygdala connectivity relative to FFA-amygdala connectivity in MoS compared to healthy controls, suggesting that neurocircuitry underlying emotion processing may be altered in MoS.

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Poster

074. Emotion: Human Emotion I

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Topic: G.03. Emotion

Support: Fulbright STEM Award for Graduate Studies
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Title: Predictability and uncertainty in the pleasure of music

Authors: ***B. P. GOLD**^{1,2,3}, M. T. PEARCE⁴, E. MAS-HERRERO¹, A. DAGHER¹, R. ZATORRE^{1,5,3}

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Abstract: Music consistently ranks among life's greatest pleasures, and prediction is widely believed to be central to its appeal. As it constantly evolves across multiple structures, music is especially well suited to establishing and manipulating predictions; musical surprises often lead to sharp increases or decreases in liking. In a previous experiment, we implemented a widely-used reinforcement learning task and algorithm in a musical decision-making context to show that music can elicit formally modeled reward prediction errors in the activity of the nucleus accumbens, perhaps driving engagement and/or pleasure. Yet the relationship between specific musical surprises and pleasure remains unclear. Isolated findings suggest that there might be an inverted-U-shaped relationship between surprise and liking, wherein music that optimally balances prediction confirmations and errors is most pleasurable - but previous manipulations of music predictability have yielded mixed results. In the present study, we therefore extend our prior research with a well-validated information-theoretic model to investigate the contributions of musical uncertainty and predictability to pleasure, and neural reward-network activity during naturalistic music listening. We presented participants with real Western musical excerpts from a wide spectrum of objective musical predictabilities and uncertainties as computed on note-by-note transition probabilities with the Information Dynamics of Music model. Listeners rated their music liking as they listened, while we monitored their neural responses during fMRI. We evaluated the liking ratings with linear and quadratic regression models, finding that a quadratic effect between predictability and liking fit the data significantly better than a linear model, therefore corroborating existing evidence of an inverted-U-shaped effect. Neuroimaging analyses illustrated separate networks responding to liking and surprise, with an interaction between these concepts in important nodes of the reward system. Together, these analyses will clarify the role of predictive processing in the human infatuation with music, broadening our understanding of abstract rewards and pleasures.

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Poster

074. Emotion: Human Emotion I

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Topic: G.03. Emotion

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Title: Inter-personal functional connectivity of central and autonomic nervous systems reflects emotional convergence during watching movies

Authors: *H. KIM, D. YEO, P. SEO, S. HER, S. CHOI, K.-H. KIM
Bio Med. Engin., Yonsei Univ., Wonju, Korea, Republic of

Abstract: Introduction: Recent studies demonstrated that physiological responses of interacting individuals become synchronized. However, it is unknown whether this inter-personal physiological synchrony occurs without an explicit face to face interaction. Here we tried to investigate the inter-personal synchronization of physiological responses of a pair of persons during watching affective movie clips simultaneously, and its relationship with the level of emotional convergence of the pair.

Methods: Sixteen pair of healthy subjects (32 subjects, 22.5 ± 1.65 years old) participated in the experiment. Each pair of subjects watched affective video clips simultaneously, while 62-channel EEGs, Galvanic skin response, photoplethysmogram, and skin temperature were recorded. Right after watching each video clip, the subjects rated their emotional response in valence and arousal levels in 9-point Likert scale. Emotional convergence scores were calculated as the inverse of absolute value of the difference between the self-ratings of the pairs in each. From the scalp EEGs, distributed cortical sources were estimated using weighted minimum norm estimation. Inter-personal functional connectivity was investigated by the phase-locking values (PLVs). For the autonomic responses, inter-subject correlation (ISC) analysis was performed. The interrelationship between the inter-personal synchrony in physiological responses and the emotional convergence scores were analyzed by Spearman correlation.

Results: The inter-personal PLVs were significantly correlated with the arousal convergence scores at right supplementary motor area and rostral middle frontal cortex, in Beta-band, and at left premotor area, anterior frontal cortex, and bilateral temporal cortex in Gamma-band ($\rho > 0.45$, $p < 0.01$). The ISC scores of HRV were significantly correlated with valence convergence scores ($\rho: 0.72$, $p < 0.001$). In addition, averaged ISC scores were significantly correlated with arousal convergence scores ($\rho: 0.75$, $p < 0.001$).

Discussion: The pair of individuals with a strong convergence of emotional arousal exhibited

strong brain functional connectivity in the anterior frontal cortex, premotor area, temporal lobe and synchrony of autonomic arousal. This imply the inter-personal synchrony of mirror neuron system activities (i.e. premotor and inferior frontal activities) reflects empathy between the two subjects. Previously, synchrony of autonomic nervous system activities was found between mother and child without physical contact. Our results on ISC may indicate autonomic mimicry occurs solely by external emotional input, without direct interaction.

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Poster

075. Emotion: Neurocircuitry I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 075.01/WW13

Topic: G.03. Emotion

Title: Encoding of fear-reward-safety cue discrimination in the infralimbic cortex

Authors: ***K. H. NG**^{1,2}, **S. SANGHA**^{1,2}

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Abstract: Expressing fear behavior in the absence of a threat is maladaptive because it decreases an organism's opportunity to seek life-sustaining substances. Learned safety signals can rescue the organism from this immobilizing state to resume exploratory behaviors. The infralimbic (IL) region of the prefrontal cortex is critical for fear extinction consolidation (Hikind & Maroun, 2008; Milad & Quirk, 2002) and fear versus safety cue discrimination (Sangha et al., 2014). IL neurons also show increased activity to an extinguished fear cue during the recall of fear extinction memory (Milad & Quirk, 2002). We thus hypothesized that IL neurons also encode for safety signals that are actively suppressing fear behavior in a situation that may be perceived as potentially dangerous. We recorded from IL neurons using multi-array electrodes during a fear-reward-safety cue discrimination paradigm that is well established in our laboratory (Sangha et al., 2013; Sangha, Greba, et al., 2014; Sangha, Robinson, et al., 2014; Ng et al., 2018). In this task, rats learn that the fear cue will result in a footshock, but when simultaneously presented with the safety cue as a compound cue (fear+safety cue), there is no footshock; male rats subsequently show high freezing to the fear cue and significantly lower freezing to the fear+safety cue. Our preliminary multi-unit data show that IL neurons increase their firing to the combined fear+safety cue when compared to the safety cue or fear cue alone, as well as increased firing to the reward cue. IL neurons also showed increased firing during reward consumption behavior. These data suggest that conditioned inhibition of fear via a safety cue and

conditioned reward seeking in response to a reward cue may both engage an overlapping neural circuit within the IL.

Disclosures: K.H. Ng: None. S. Sangha: None.

Poster

075. Emotion: Neurocircuitry I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 075.02/WW14

Topic: G.03. Emotion

Support: Swiss National FOundation 31003A_160325

Title: The orbitofrontal cortex projects to the parvafox nucleus of the ventrolateral hypothalamus

Authors: *M. R. CELIO¹, A. BABALIAN¹, S. EICHENBERGER¹, A. BILELLA¹, F. GIRARD¹, V. SZABOLCSI¹, D. ROCCARO¹, G. ALVAREZ-BOLADO², C. XU³

¹Univ. of Fribourg, Fribourg, Switzerland; ²Inst. of Anat. and Cell Biol., University of Heidelberg, Germany; ³Friedrich Miescher Inst., Basel, Switzerland

Abstract: Although connections between the orbitofrontal cortex and the lateral hypothalamus have been recognized in the past, the precise targets of the descending fibres have not been identified, owing to the absence of obvious cell aggregates in this diencephalic extension of the reticular formation.

By means of viral tracer-transport experiments in rodents, we demonstrate neurons of the lateral (LO) and the ventrolateral (VLO) orbitofrontal cortex (OFC) to project collateral axons to a discrete but distinct horizontally-oriented cylindrical nucleus in the lateral hypothalamus, namely, the parvalbumin- and Foxb1-immunoreactive (“parvafox”) nucleus.

The loose bundle of fine, straight, descending collaterals arises at the level of the tuberal hypothalamus, from thick OFC-derived axons coursing in the internal capsule. They contact the neurons of the parvafox nucleus through garland-shaped, VGlut2-immunoreactive “boutons”. In its further caudal course, the contingent of OFC-axons projects collaterals that terminate in two elongated neuronal columns – the SU3 – and the PV2 nuclei – which lie ventral to the aqueduct at the border of the periaqueductal grey matter (PAG). Here, the OFC-endings overlap with terminals of the VGlut2-immunoreactive boutons deriving from the hypothalamic parvafox nucleus itself.

The selective targeting of the parvafox nucleus by the OFC-projection, and the overlapping of their terminal fields within the PAG, suggest that the two cerebral sites are closely coupled. An involvement of this OFC-driven circuit in the autonomic manifestation of a behavioural event is conceivable.

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Poster

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Program #/Poster #: 075.03/XX1

Topic: G.03. Emotion

Support: Wellcome Trust
King Fahad Medical City

Title: Functional and behavioural investigation of amygdala to hippocampus connectivity

Authors: *R. ALSUBAIE¹, A. F. MACASKILL², E. MENICHINI²
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Abstract: The Basomedial Amygdala (BMA) and ventral hippocampus (vHPC) are crucial for the appropriate behavioural response to affective cues. Classical studies have shown dense innervation of BMA axons in vHPC, but the functional properties of the circuit remain unexplored. Through a series of anatomical, functional and behavioural experiments we describe a specialised microcircuit between the BMA and vHPC. First, using anterograde and retrograde neural tracers, we confirmed reciprocal anatomical connectivity between the vHPC and BMA. Next, using ChR2-assisted circuit mapping we find robust excitatory and inhibitory synaptic input from BMA to vHPC, with interesting inhibitory circuit architecture. In order to begin to probe the behavioural role of this circuit we next manipulated the activity of BMA to vHPC axons in vivo during free behaviour, where we found this projection is sufficient to influence affective behaviour. Overall we show that BMA projection neurons anatomically and functionally connect to vHPC pyramidal neurons, and that this circuit may be involved in the control of appropriate affective behaviour. Future investigation will focus on the understanding the potential role of this circuit in vivo.

Disclosures: R. Alsubaie: None. A.F. MacAskill: None. E. Menichini: None.

Poster

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Location: SDCC Halls B-H

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Program #/Poster #: 075.04/XX2

Topic: G.03. Emotion

Title: Towards a role of inhibition in amygdalo-hippocampal emotion-related circuitry

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Abstract: Amygdala is a structure related to emotional responses, survival and motivation. It is intrinsically linked to learning and memory. Some disorders like anxiety, posttraumatic stress disorder and obsessive-compulsive disorder are associated to changes in the information process in this region. The synaptic inhibition is responsible for modulating principal neurons and others interneurons activity as well, filtering selectively the synaptic excitation, which determines the information flow. In this work, we investigated how long range inhibitory projections from the ventral hippocampus can modulate the amygdala activity by using viral tracers to identify the connections and light stimulation combined with patch clamp technique. We therefore used a transgenic Chrna2-Cre and a PV-Cre mouse line to target such neurons. Using Gabazine to block inhibitory responses, we confirmed the GABAergic stimulation can no longer generate responses in the post-synaptic terminal. Taken together, our data characterized the existence of a disynaptic amygdalo-hippocampal circuit mediated by long range GABAergic neurons.

Disclosures: M. Lima: None.

Poster

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Location: SDCC Halls B-H

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Program #/Poster #: 075.05/XX3

Topic: G.03. Emotion

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Title: Synchronized type-2 theta oscillations in the reciprocal cingulo-amygdala circuits drive observational fear in mice

Authors: *S.-W. KIM¹, M. KIM¹, J. BAEK¹, G. GANGADHARAN¹, C. LATCHOUMANE¹, T. CHO¹, J. BYUN¹, D.-S. KIM³, H.-S. SHIN²

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Abstract: Observational fear relies on the coordinated activity in the cingulo-amygdala circuits, yet the underlying neural mechanism and substrates allowing long-range functional connections during observational fear expression remains unclear. Here, we found that mice with a knockout or right anterior cingulate cortex (ACC)-specific knockdown of phospholipase C- β 1 (PLC- β 1) showed impaired observational fear, whereas silencing of PLC- β 1 in the left ACC, prelimbic, and infralimbic cortex had no effect. In the local field potential recording, power and phase synchrony of low-frequency theta rhythms in the range of 4-8 Hz were decreased in the ACC and basolateral amygdala (BLA) of ACC-specific PLC- β 1 knockdown observers during observational fear. Suppression of type-2 theta rhythms by optogenetic inhibition of medial septal GABAergic neurons projecting to the hippocampus decrease freezing level during observational fear. Furthermore, optogenetic inhibition of the reciprocal excitatory connections between the ACC and the BLA suppressed observational fear without affecting classical fear conditioning. Thus, these results suggest that type-2 theta oscillations in the reciprocal cingulo-amygdala circuits drive observational fear.

Disclosures: S. Kim: None. M. Kim: None. J. Baek: None. G. Gangadharan: None. C. Latchoumane: None. T. Cho: None. J. Byun: None. D. Kim: None. H. Shin: None.

Poster

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Program #/Poster #: 075.06/XX4

Topic: G.03. Emotion

Support: 109005/Z/15/Z
109005/Z/15/A

Title: Parallel ventral hippocampal projections to PFC and NAc

Authors: *C. SANCHEZ BELLOT, A. F. MACASKILL
Univ. Col. London, London, United Kingdom

Abstract: The subiculum is the main output region of the hippocampus. Despite targeting multiple downstream regions, its efferents are thought to be organised as parallel projections,

with any one neuron targeting only one downstream region. This raises the possibility that different projections have specific contributions to behaviour. Here, we focus on projections from the ventral subiculum (vS) to the prefrontal cortex (PFC) and nucleus accumbens (NAc), which are thought to be differentially involved in mediating affective behaviour, although this is yet to be conclusively demonstrated. Through molecular, cellular and circuit investigation, we found marked differences in electrophysiological and morphological properties among the different projection populations. Ongoing experiments involve an intersectional strategy to specifically target NAc and PFC-projecting cells in ventral subiculum and to characterise their distinct synaptic connectivity, their unique contributions to hippocampal output, and their differential roles in affective behaviour.

Disclosures: C. Sanchez Bellot: None. A.F. MacAskill: None.

Poster

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Topic: G.03. Emotion

Support: FRQS
NSERC

Title: Hippocampal inputs to the nucleus accumbens promote consummatory pleasure

Authors: *A. YANG, J. A. MENDOZA, C. LAFFERTY, J. P. BRITT
McGill Univ., Montreal, QC, Canada

Abstract: Anhedonia, the inability to experience pleasure, is a prevalent symptom in many psychiatric disorders such as depression and schizophrenia. The nucleus accumbens (NAc) has been implicated in the sensation of pleasure in both human fMRI and rodent pharmacology studies. In rats, mu-opioid receptor agonists targeted to the rostral NAc shell increase consummatory pleasure, however the physiological underpinnings of this phenomenon are poorly delineated. Mu-opioid receptor stimulation alters NAc physiology in a variety of ways, including by reducing glutamate input in a pathway-specific manner. To determine the extent to which specific glutamate inputs can influence consummatory pleasure, we employed optogenetic tools in mice to manipulate input activity in the NAc from the ventral hippocampus, basolateral amygdala, and midline thalamus. We used licks per bout as an objective measure of pleasure, which is the average number of licks in each bout of liquid sucrose consumption. We report that high-frequency stimulation (16-48Hz) of any glutamatergic input to the NAc terminates feeding, whereas 1Hz stimulation specifically of hippocampal input significantly increases licks per bout. It is unlikely that this effect relates to a change in enkephalin-containing NAc neuron activity, as

we found no causal relation between its activity and consummatory pleasure. However, low-frequency stimulation of enkephalin-containing NAc neurons slightly increases total consumption, possibly via an inhibition of the direct pathway NAc neurons that are known to facilitate feeding. Current experiments aim to characterize how NAc output activity influences consummatory pleasure, with the hope that a better understanding of NAc-generated pleasure will help guide treatment development efforts for pathologies involving anhedonia.

Disclosures: A. Yang: None. J.A. Mendoza: None. C. Lafferty: None. J.P. Britt: A. Employment/Salary (full or part-time):; McGill University.

Poster

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Topic: G.03. Emotion

Support: Oklahoma-INBRE Grant P20GM103447
Presbyterian Health Foundation

Title: Neuroligin-2 organizes inhibitory synaptic transmission in the lateral septum to regulate stress-induced neuronal activation and anxiety-related behavior

Authors: *E. TROYANO-RODRIGUEZ^{1,2}, E. MARTIN¹, C. R. WIRSIG-WIECHMANN^{1,2}, M. AHMAD^{1,2}

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Abstract: The lateral septum (LS) is a subcortical forebrain structure that is important for the regulation of affective behaviors including anxiety, aggression, social recognition, and food seeking. Even though substantial previous work has shown that the LS plays critical roles in regulating various affective behaviors, the molecular organization of its synapses remains largely unstudied. It is also unknown which molecules modulate the balance of excitatory and inhibitory synaptic transmission (E/I ratio) in the LS and how alteration of this ratio contributes to the ability of this subcortical region to respond to salient experiences and regulate behavior. This lack of information stands in contrast to the extensive published work regarding the role of E/I balance (and imbalance) in the neocortex in affecting information processing and animal behavior. In this study, we have manipulated E/I balance in the LS by conditional deletion of neuroligin-2 (NL2), a postsynaptic cell adhesion protein linked to neuropsychiatric disorders. Absence of NL2 in the LS in the mature mouse brain resulted in selective postsynaptic impairment of inhibitory synaptic transmission. The resulting E/I imbalance altered the responsiveness of LS neurons to stress as observed with staining for immediate early gene *c-fos*.

Furthermore, the enhanced E/I ratio in the LS led to impaired stress-induced activation of downstream hypothalamic nuclei, which was associated with altered avoidance behavior of the animals in the elevated plus maze. These results provide information about the function of NL2 in the LS and demonstrate that the E/I imbalance in this subcortical region in the absence of NL2 produces major impairments in the processing of behavioral input and regulation of anxiety-related behavior.

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Poster

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Title: Transforming sensory cues into aversive emotion by septal-habenular pathway

Authors: ***G. ZHANG**¹, **S. LI**², **W. ZHONG**³, **Y. XIONG**¹, **L. I. ZHANG**², **H. TAO**²

¹Dept. of Neurobio., Third Military Med. Univ., Chongqing City, China; ²USC Keck Sch. Med., Los Angeles, CA; ³Southern Med. Univ., GuangDong, China

Abstract: Emotions evoked by environmental cues are important for animal survival and life quality. However, neural circuits responsible for transforming sensory signals to aversive emotion and behavioral avoidance remain unclear. Here, we found that medial septum (MS) mediates the aversion induced by sensory stimuli of different modalities. Ablation of glutamatergic or GABAergic MS neurons results in impaired or strengthened aversion respectively. Optogenetic activation of the two cell types results in place-avoidance and -preference, respectively. Cell-type specific screening reveals that glutamatergic MS projections to the lateral habenula (LHb) are responsible for the induction of aversion, which can be antagonized by GABAergic MS projections to LHb. Additionally, the sensory induced place avoidance is facilitated by enhanced locomotion, mediated by glutamatergic MS projections to the preoptic area. Thus, MS can transmit innately aversive signals via a bottom-up multisensory

pathway and produce concurrent emotional and motivational effects, allowing animals to efficiently avoid aversive environments.

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Poster

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Topic: G.03. Emotion

Support: NIH Grant R01 MH106532
NIH Grant T32 NS099578

Title: The role of pituitary adenylate cyclase-activating polypeptide in the lateral habenula

Authors: *M. R. LEVINSTEIN, Z. K. LEWIS, J. F. NEUMAIER
Psychiatry and Behavioral Sci., Univ. of Washington, Seattle, WA

Abstract: The lateral habenula (LHb) is a small nucleus in the epithalamus of the brain with three main output pathways - to the dorsal raphe nucleus (DRN), the ventral tegmental area (VTA), and the rostromedial tegmental nucleus (RMTg). The LHb is strongly activated by stress and other aversive stimuli and regulates the activity of the dopamine and serotonin systems via distinct, non-overlapping, output pathways that are important for the behavioral encoding of stress and addiction. Our previous work indicates that the LHb to DRN pathway is responsible for producing an antidepressant effect when the lateral habenula is chemogenetically inhibited whereas projections to VTA or RMTg were not involved. We hypothesized that the LHb neurons constituting these pathways are phenotypically distinct and are involved in different components of stress-related behaviors. While primarily glutamatergic, this nucleus also expresses numerous neuropeptides which may be beneficial as therapeutic targets. One such peptide is pituitary adenylate cyclase-activating polypeptide (PACAP), which is involved in both circuit and cellular stress responses. Although, PACAP has been shown to be elevated after stress, to date no one has investigated its role within LHb neurons. In this study, we examine the pathway specificity of PACAP RNA expression first by retrogradely labeling neurons and performing fluorescent *in situ* hybridization to visualize co-localization following acute swim stress. Preliminary results indicate that PACAP expression may not be pathway specific; however, PACAP expression appears to increase in the LHb following acute stress. Additionally, we utilize a combination of mouse genetic models and cre-inducible viruses to investigate the role of the PACAP expressing neurons in the LHb. We anterogradely label these neurons by using a cre-dependent synaptophysin-EGFP fusion virus, which preferentially labels presynaptic terminals in a

PACAP-cre mouse line and co-stain for Gad67 or TPH2 to label GABAergic or serotonergic target neurons. We are also investigating the pathway or cell-type specific mRNA expression by utilizing a cre-dependent RiboTag viral vector to extract mRNA following stress in rats and mutant mice, respectively.

Disclosures: M.R. Levinstein: None. Z.K. Lewis: None. J.F. Neumaier: None.

Poster

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Topic: G.03. Emotion

Support: NIH K01DA039999 (S.G.N)

Title: Analysis of RiboTag mRNA in lateral habenula projection neurons

Authors: *S. G. NAIR, A. L. LESIAK, A. D. CHISHOLM, M. M. ESTABROOK, P. SILVA, J. F. NEUMAIER

Psychiatry and Behavioral Sci., Univ. of Washington, Seattle, WA

Abstract: The lateral habenula (LHb), an epithalamic nucleus is known to be involved in the processing of aversive information. The LHb receives inputs from limbic brain regions and the prefrontal cortex and projects to the dopaminergic ventral tegmental area (VTA), the serotonergic dorsal and median raphe nuclei (DRN and MRN) and the GABAergic rostromedial tegmental nucleus (RMTg), among other brain regions. While majority of LHb projection neurons are known to be glutamatergic, further characterization of their gene expression is mostly lacking. Here, we used an intersectional dual virus DIO strategy to selectively express HA-tagged Rpl22 protein (RiboTag) to interrogate mRNA's undergoing active translation in LHb neurons projecting selectively to the VTA, DRN or the RMTg. Male Long-Evans rats were injected with a doubly floxed adeno-associated virus expressing RiboTag into the LHb and a canine adenovirus (CAV2) expressing Cre into either the VTA, DRN or the RMTg. CAV2-Cre efficiently transduces axon terminals in the VTA, DRN and the RMTg and is retrogradely transported to neuronal cell bodies in the LHb where it flips the RiboTag into proper orientation to allow transcription. Three weeks after intracranial injections, rats were decapitated, and ~2mm punches of the LHb were dissected bilaterally. The tissues were homogenized, incubated with an anti-HA antibody, purified with magnetic bead based immunopurification and RNA was isolated. Approximately 17-26 ng of RNA was obtained per rat. Quantitative PCR and RNA seq analysis will be performed on the collected RNA to identify genes that are differentially expressed in LHb neurons projecting to the VTA, DRN or the RMTg under basal conditions and following operant cocaine self-administration.

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Poster

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Topic: G.03. Emotion

Support: P50 MH106428
R01 MH106532
T32 DA007278

Title: DREADD mediated inhibition of the Lateral Habenula to Dorsal Raphe output pathway has antidepressant effects in rats

Authors: *K. COFFEY¹, R. MARX², E. VO¹, J. F. NEUMAIER³

¹Univ. of Washington, Seattle, WA; ²Univ. of Washington, Bellingham, WA; ³Dept Psych, Univ. Washington, Seattle, WA

Abstract: The lateral habenula (LHb) is small epithalamic region that acts as a key gateway between limbic forebrain neurons and the midbrain monoaminergic systems. Over the past decade there has been resurgence of interest in the LHb as evidence has emerged that it plays a central role in encoding rewarding and aversive stimuli and in neuropsychiatric diseases, including mood disorders. Recently, we found that expressing an inhibitory DREADD (hM4Di) in the LHb of rats and administering the otherwise inert ligand, clozapine-N-oxide (CNO) produced an antidepressant-like effect in the modified forced swim test (mFST) but the downstream target of LHb neurons mediating this effect is not known. There are three important targets of glutamatergic outputs from LHb: ventral tegmental area (VTA), rostral medial tegmental nucleus (RMTG), and dorsal raphe nucleus (DRN). Isolating the pathway responsible for this effect could provide an excellent target for developing novel antidepressant treatments with fewer off-target effects. In order to study the effect of inhibiting these pathways in isolation we utilized an intersectional viral vector strategy: AAV-EF1 α -DIO-HM4Di injected into LHb, and CAV2-Cre (a retrograde viral vector) injected into one of the three target areas in 16 rats per pathway. We utilized the mFST in a 3x2 design to determine if inhibiting any (or all) of the three pathways are sufficient to confer an antidepressant-like effect. We developed a novel automated activity scoring algorithm to provide unbiased behavioral output which compared well to conventional time sampling analysis of the mFST. A small number of “anatomical misses”, that showed no LHb DREADD expression, generated a useful negative control group. The only treatment difference between groups was injection of either vehicle or CNO. Our results suggest that inhibiting the LHb to DRN pathway provides an anti-depressant effect, while inhibition of

the other pathways does not. Animals with hM4Di in the LHb \rightarrow DRN pathway that were treated with CNO showed less inactivity during the mFST, as well as increased swimming and climbing. These results supports the idea that inhibiting the LHb to DRN pathway provides animals with resilience to the behavioral despair normally induced by the mFST, and also opens up the LHb to DRN pathway to manipulation by highly specific therapeutics for the treatment of depression.

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Poster

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Topic: G.03. Emotion

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Title: Projections from the posterior insular cortex mediate top-down control of motivated behaviors

Authors: ***D. A. GEHRLACH**¹, N. DOLENSEK¹, A. S. KLEIN¹, M. JUNGHAENEL¹, A. MATTHYS¹, N. REDDY VAKA¹, T. GAITANOS¹, R. ROY CHOWDHURY¹, K.-K. CONZELMANN², N. GOGOLLA¹

¹Circuits for Emotion Res. Group, Max Planck Inst. of Neurobio., Martinsried, Germany; ²Max von Pettenkofer-Institute & Gene Center, Med. Fac., Ludwig-Maximilians-University Munich, Munich, Germany

Abstract: A large body of human imaging studies has identified the insular cortex as a core region affected across various psychiatric conditions, such as anxiety disorders, major depressive disorder or addiction. Despite this important role, the neuronal circuit mechanisms underlying insula function remain unknown. Here we define a role for the posterior insular cortex in mediating aversive feeling states and regulating motivated behaviors in mice. Optogenetic activity manipulations of insular projection neurons produced behavioral and bodily changes consistent with negative feelings and revealed bidirectional and sustained effects on motivated behaviors biasing them towards avoidant-, defensive- and fear-related. Viral tracings were used to map the whole brain in- and outputs of the posterior insula uncovering the anatomical organization underlying the observed responsiveness, and providing subcortical candidate regions for mediating the behavioral alterations. To dissect the contribution of different top-down target regions to the observed emotional responses, we found a central amygdala-projecting pathway to promote changes in respiration and fear-related behaviors, resulting in general behavioral inhibition. Activation of an independent nucleus accumbens-projecting

pathway specifically interrupted ongoing consummatory behaviors and induced anhedonic effects in a subset of susceptible animals. Together, our findings identify the posterior insular cortex as a potent top-down modulator of motivated behaviors and provide a first entry point towards a better understanding of how alterations in insula circuitry may contribute to the pathology of neuropsychiatric conditions.

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Poster

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Program #/Poster #: 075.14/XX12

Topic: G.03. Emotion

Support: Washington University in St. Louis

Title: Dissecting the behavioral role of dynorphin-expressing central amygdala neurons

Authors: **M. C. WALICKI**¹, M. R. NORRIS^{2,1}, G. B. GEREAU¹, ***J. G. MCCALL**¹

¹Anesthesiol., Washington Univ. in St. Louis, Saint Louis, MO; ²Purdue Univ., West Lafayette, IN

Abstract: The central amygdala (CeA) is a critical structure in regulating the emotional response to stress, pain, and drugs of abuse. As a molecularly heterogeneous structure, many cell-types have been identified in the CeA, but little is understood about the contribution of these molecularly-defined neurons to behavior. Here, we aim to dissect the behavioral role of CeA neurons expressing the neuropeptide dynorphin (Dyn+), the endogenous ligand for the kappa opioid receptor. Using Cre-dependent tdTomato reporter mice crossed to mice expressing Cre under the prodynorphin promoter (pDyn-Cre), we genetically identify Dyn+ neurons and report distinct patterns of c-fos expression, a secondary marker of neuronal excitation, following acute 30-minute restraint stress paradigm, in response to a Complete Freund's Adjuvant inflammatory pain challenge, acute ethanol exposure, and to palatable food exposure. To test the sufficiency of the CeA-Dyn+ neurons to drive behaviors, we used in vivo optogenetics to photostimulate dynorphinergic neurons in the central amygdala in a real-time place testing paradigm, food consumption paradigm, open field test of anxiety-like behavior, and hot plate test of thermal sensation. The c-fos studies suggest that CeA-Dyn+ neurons may not acutely respond to aversive stimuli. Additionally, in the real-time place testing paradigm, we find that selective photostimulation of CeA-Dyn+ neurons does not drive rewarding or aversive behaviors. Additionally, acute activation of CeA dynorphinergic neurons does not appear to affect food

consumption in sated or food-deprived states. However, activation of the CeA dynorphinergic neurons in an open field testing paradigm and hot-plate testing may acutely affect anxiety-like and nocifensive behaviors. Understanding the role of the central amygdala dynorphin/kappa opioid system relative to chronic stress, pain, and drug taking may provide insight into therapeutic targets and strategies for these neurological and neuropsychiatric disorders.

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Poster

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Topic: G.03. Emotion

Support: DA035371
DA041482

Title: Mesointerpeduncular circuitry and dopaminergic control of affective state

Authors: ***S. R. DEGROOT**, R. ZHAO-SHEA, P. D. GARDNER, A. R. TAPPER
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Abstract: Anxiety disorders are the most common class of mental disorders. Anxiety is an affective state classically governed by the prefrontal cortex, hippocampus, and the extended amygdala, which includes the bed nucleus of the stria terminalis (BNST). Previous studies suggest that stimulation of glutamatergic BNST efferents in the ventral tegmental area (VTA) is anxiogenic. Further, the VTA can exhibit control of affective state by heterogeneous efferent terminal activation in certain brain regions. Recently, we showed that the mesointerpeduncular circuit, which consists of VTA dopaminergic (DAergic) neurons that innervate the interpeduncular nucleus (IPN), is an important component in nicotine withdrawal-induced anxiety. The current study further explores the mesointerpeduncular circuitry, specifically DAergic control of the IPN in drug naïve mice. Using cell-attached patch-clamp electrophysiology in acute mouse midbrain slices, we defined two neuronal populations of the ventral IPN (vIPN) by input resistance and response to exogenous application of DA. “Type A” neurons displayed low input resistance and responded to DA with an increase in spontaneous action potential frequency (sAPF), while “Type B” neurons exhibited a higher input resistance and responded to DA with a decrease in sAPF. Whole-cell patch clamp recordings revealed changes in excitatory postsynaptic current frequency, but not amplitude in IPN neurons during VTA terminal stimulation suggesting that DA acts presynaptically to modulate IPN inputs. Using viral mediated gene delivery and CRE-Lox technology, we expressed channelrhodopsin-2

(ChR2) specifically in putative DAergic VTA neurons of DA transporter (DAT)-CRE mice. Optogenetic stimulation of VTA neurons resulted in sAPF changes prominently in the caudal IPN. These responses were blocked by D1-family DA receptor (DRD1) antagonists and were localized to areas containing putative DRD1-expressing cell bodies. Dopaminoceptive caudal IPN neurons exhibited significantly higher input resistance compared to Type A or B neurons suggesting a third neuronal subtype, "Type C". Optogenetic stimulation of putative DRD1-expressing Type C terminals in the presence of TTX and 4AP in the vIPN of DRD1-Cre mice resulted in EPSC frequency changes in Type A and Type B neurons that phenocopied the response to exogenous DA application. Under these conditions, combined GABA-A and GABA-B receptor antagonists were sufficient to block EPSC frequency changes suggesting Type C neurons are primarily GABAergic. Together, our results identify a novel microcircuit by which the VTA controls activity of the IPN to potentially modulate affective behavior.

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Poster

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Title: Cortical microcircuits underlying ticklishness in rat somatosensory cortex

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Abstract: Tickling induced behavior is a common feature of social play interactions, in particular during childhood and adolescence. Such behaviors include bursts of vocalizations that are associated with a positive valence and defensive motor actions. Both behaviors have been reported in humans and rats (Burgdorf and Panksepp, 2001) as responses to tickling of specific body parts. Although the precise neuronal mechanisms of such behaviors are not known, recent findings show robust neuronal correlates of ticklishness in deep layers of trunk somatosensory cortex (Ishiyama and Brecht, 2016). An initial analysis of the tickling responses revealed that the vocalizations were closely linked to the experimenter's finger movement. Such direct coupling of touch and vocalizations is in line with microstimulation results, which suggested a direct link between somatosensory cortical activity and vocalization (Ishiyama and Brecht, 2016). In order to determine the microcircuits that mediate ticklishness we take advantage of the differential ticklishness of body parts (Schwartz et al., 2007). To quantify such ticklishness differences, we

assessed ticklishness of 10 different body parts by analyzing vocalization rates during tickling in various experimental conditions. While there were slight differences in ticklishness (measured by vocalization rate) as a function of experimental condition (the animal being flipped or not) we observed robust differences between ticklish body parts (trunk regions: belly and neck) and non-ticklish body parts (e.g. fore-paw, hind-paw and tail). At the moment we determine if the differential ticklishness of body parts is reflected or caused by a differential connectivity of different sub-regions of somatosensory cortex. As a first step, we injected the anterograde tracer biotinylated dextran amine (BDA) in trunk somatosensory cortex and analysed whole brain coronal sections. We found strong cortico-cortical projections to S2, M1 and M2 and weaker projections to perirhinal and ectrorhinal cortex. As expected, we also found subcortical projections to the VPM and P_{Om} in the thalamus. Interestingly, anterograde labelling revealed projections to subcortical regions associated with reward and emotional processing (ncl. accumbens) and vocalizations (periaqueductal gray, pretectal nuclei). Our results suggest that the trunk somatosensory region might have specific prerequisites for tickling induced vocalizations. In ongoing work, we plan to test this hypothesis using various experimental strategies.

Disclosures: **E. Maier:** None. **S. Ishiyama:** None. **M. Brecht:** None.

Poster

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Title: Expression pattern of neural activity markers induced by therapeutic effects of extinction after stress

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Abstract: Cognitive behavioral therapy (CBT) is an effective treatment for both major depressive disorders (MDD) and posttraumatic stress disorder (PTSD). However, the neurobiological mechanisms underlying the treatment efficacy have remained unclear. Recently, our lab discovered that a cognitive behavioral intervention, namely fear extinction learning, which resembles a type of CBT called exposure therapy, ameliorated the deficits in cognitive

flexibility and active coping behavior induced by chronic unpredictable stress (CUS), an animal model that mimics many of the shared dimensions of PTSD and MDD in rats. To determine the neural substrates underlying the effectiveness of extinction therapy, we are examining the protein expression of immediate early genes (c-fos and Arc) and marker for neuronal activity (pS6) in different rat brain regions by immunohistochemistry. Currently, we found that extinction therapy significantly evoked c-fos, arc and pS6 expression in infralimbic of mPFC along the rostro-caudal axis compared with control groups. We will continue to examine those protein expressions in the other brain structures. These results will provide evidences for us to further explore that the neural circuits which might contribute to the beneficial effects of extinction therapy on CUS-induced deficits.

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Poster

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Title: Optogenetic activation of medial prefrontal cortex projections to the dorsal periaqueductal gray decreases reward consumption

Authors: *H. NOAMANY¹, C. SICILIANO¹, X. CHEN¹, J. WANG¹, Y. LEOW¹, E. Y. KIMCHI³, C. M. VANDER WEELE², K. M. TYE²

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Abstract: An imbalance between the motivation to seek rewards and avoid punishments can lead to a number of emotional and motivational disorders including compulsive reward-seeking. We have previously shown that medial prefrontal cortex (mPFC) cells projecting to the dorsal periaqueductal gray (dPAG) encode aversive stimuli and can serve as a punishment. However, we lack an understanding of how mPFC-dPAG neurons mediate punishment. It is yet unclear if this effect is mediated by altered perception of stimuli, initiation of avoidance motor programs,

or modulation of internal states. Here, we performed a battery of behavioral tests including elevated plus-maze, light-dark box, extinction of operant alcohol self-administration, and microstructural analysis of licking behavior, in male C57BL/6J mice. For each test, we activated or silenced mPFC-dPAG neurons in a temporally specific manner using channelrhodopsin-2 (ChR2) or halorhodopsin (NpHR), respectively, and behavioral outputs were compared to fluorophore-only control animals (eYFP). We found that while excitation of mPFC-dPAG neurons drives place avoidance in a real-time place preference (RTPP) assay (eYFP, n=8; ChR2, n=10; $p < 0.05$), neither inhibition nor excitation altered anxiety-related behavior or movement velocity in elevated plus-maze or light-dark box assays. Additionally, pairing excitation (eYFP, n=4; ChR2, n=8) or inhibition (eYFP, n=5; NpHR, n=8) of mPFC-dPAG neurons with reward port entry during extinction of alcohol self-administration behavior had no effect on extinction of the operant response. Interestingly, while photoexcitation is sufficient to act as a punishment and decrease alcohol consumption, excitation did not produce readily apparent alterations to the within-bout microstructure of licking behavior (e.g. inter-lick interval and lick duration). However, latency to the first alcohol lick bout was increased after repeated sessions/days of pairing excitation with lick onset (eYFP, n=6; ChR2, n=9; $p < 0.05$). In each session, stimulation did not occur until a lick was initiated, thus increased latency to initiate the first lick suggests that activation of mPFC-dPAG neurons in previous sessions leaves a lasting impact on alcohol consumption. Together, our data demonstrate a broad role of mPFC-dPAG neurons, whereby activation of these cells can imbue lasting, non-anxiogenic, negative value on unconditioned stimuli, and suggest that effects on alcohol consumption do not occur via gustatory or motoric mechanisms.

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Poster

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Title: Thalamic filtering of task-relevant information to amygdala across changing contingencies

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Abstract: The ability to accurately predict the motivational significance of environmental stimuli under changing conditions is critical for everyday life. Valence processing, a term describing this capacity for precise differentiation of stimuli predicting positive or negative outcomes is fundamental for advantageously navigating dynamic environments. Although The medial geniculate nucleus of the thalamus (MGN) is often thought of as a sensory relay station and basolateral amygdala (BLA) the first site of associative learning, these assumptions have not been directly tested. In this study, we ask the following questions: Does valence processing occur in MGN? What information does MGN transmit to BLA across learning? Do ensembles in MGN and BLA encode contingency contexts? To investigate the neural bases of this process, we used a task wherein two auditory stimuli predicted rewards or punishments (Pavlovian discrimination), followed by an unsignaled reversal of the outcomes associated with each conditioned stimulus (CS). We confirm the long-held but previously unproven belief that MGN transmits robust auditory CS information to BLA during learning, with ~80% of BLA-projectors encode CS information during Pavlovian discrimination. Our results also demonstrate that BLA-projecting MGN cells (n=28) are more task-responsive than the overall MGN population (Binomial Distribution test, n=132/192 Unidentified MGN neurons; n=27/28 Photoidentified MGN-BLA neurons, p<0.0001) and encode a more uniform signal about task-relevant CS information than the overall MGN population (Binomial Distribution test, n=96/192 Unidentified MGN neurons; n=22/28 Photoidentified MGN-BLA neurons, p<0.0001). In order to characterize this circuit during associative learning, we employed simultaneous multi-site single-unit *in-vivo* electrophysiology with circuit-specific optogenetic photoidentification in mice during a multi-session Pavlovian discrimination task (MGN units n=220, BLA units n=90, mice n=12). This allowed for simultaneous characterization of MGN and BLA encoding as well as photoidentification of both BLA-projecting cells in MGN and those downstream BLA cells receiving input. Upon contingency reversal, we find that distinct populations of neurons in both the MGN and the BLA selectively encode reward-predictive and punishment-predictive cues. This suggests that the MGN-BLA circuit is actively engaged in a hierarchical representation of positive and negative valence in a contingency-dependent manner.

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Poster

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Title: Cortical-brainstem projections gate compulsive alcohol drinking

Authors: *C. SICILIANO¹, X. CHEN¹, H. NOAMANY¹, J. WANG¹, Y. LEOW¹, E. Y. KIMCHI³, C. M. VANDER WEELE², K. M. TYE²

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Abstract: Perturbations in emotional and motivational valence processing can manifest as a wide array of neuropsychiatric disease states such as anxiety, depression and addiction. Elucidating the neurobiological underpinnings of individual variation in the development of alcohol use disorders is an area of great interest. Alcohol-induced plasticity in medial prefrontal cortex (mPFC) has been implicated in compulsive alcohol drinking behaviors; however, we have little understanding of the specific circuits involved. Here, we sought to dissect the role of mPFC cells projecting to dorsal periaqueductal gray (dPAG), which have recently been implicated in the processing of aversive events, in compulsive alcohol drinking. We used cellular resolution calcium imaging to assess the activity of mPFC-dPAG neurons (animals, n=8; cells, n=300-400 per day; 12 sessions) during a novel Pavlovian alcohol conditioning task. Using this task, we tested for compulsive alcohol consumption before and after two weeks of binge alcohol exposure. Binge drinking produced wide individual differences in compulsive alcohol drinking, whereby approximately 50% of animals continued to consume high levels of alcohol, despite adulteration with the bitter tastant quinine, after binge exposure, but not before. Both high and low drinking phenotypes showed decreased calcium activity in mPFC-dPAG neurons during alcohol consumption. Surprisingly, the magnitude of inhibitory responses in mPFC-dPAG neurons during the first alcohol drinking session was positively correlated with the expression of binge drinking-induced compulsive alcohol consumption three weeks after the initial exposure session (n=8, p<0.01). To test causality of mPFC-dPAG activity in compulsive drinking, we used

a closed-loop optogenetic approach to photoinhibit mPFC-dPAG neurons during licking for alcohol with quinine. Inhibition conferred a compulsive phenotype, even in animals with minimal prior alcohol exposure (eYFP, n=4; halorhodopsin, n=9; $p < 0.001$). Conversely, closed-loop optogenetic activation of mPFC-dPAG neurons paired with licking for alcohol decreased consumption (eYFP, n=6; channelrhodopsin-2, n=9, $p < 0.01$), demonstrating that activation of this pathway is sufficient to recapitulate some of the effects of quinine on alcohol intake. Together, our results support a model where inhibition or activation of the mPFC-dPAG circuit attributes positive or negative valence to unconditioned stimuli, respectively. Binge drinking reduces the sensitivity of this cortical-brainstem pathway to punishment in the context of alcohol drinking, thereby driving compulsive drinking in a subset of animals.

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Poster

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Title: Homeostatic signals for social and appetitive stimuli interact in DRN dopamine neurons

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Abstract: Both positive and negative emotional states can drive social behavior of multiple forms (e.g. investigation, affiliation, aggression). We recently identified a functional role for dorsal raphe nucleus (DRN) dopamine (DA) neurons, as optogenetic activation of DRN DA

neurons in mice promoted social preference, but also elicited place avoidance. This suggests a negative drive-induced social motivation, which we speculate is analogous to a loneliness-like state. However, the question remained - how do DRN DA neurons act through downstream targets to mediate these behavioral changes?

We have now performed projection-specific ChR2-mediated optogenetic activation to investigate the functional role of DRN DA input to the bed nucleus of the stria terminalis (BNST) and central amygdala (CeA). We find that DRN^{DA}-CeA photostimulation promoted social preference in the 3-chamber sociability assay (n=20, p=0.002), in a manner predicted by social rank (Pearson's correlation, $r^2=0.29$, p=0.01). In contrast, DRN^{DA}-BNST photostimulation induced a trend toward real-time place avoidance (n=22, p=0.09). To characterize the connectivity of DRN DA neurons, we have used transgenic mouse lines, combined with viral tracing strategies and immunohistochemistry. Specifically, using Cholera Toxin subunit B (CTB), we find that 26% (n=135/512 cells, 3 mice) of tyrosine hydroxylase positive (TH+) DRN DA neurons projecting to the BNST and CeA collateralize to innervate both regions.

To assay the natural activity of DRN DA neurons, we previously used *in vivo* fiber photometry (combined with the fluorescent calcium indicator GCaMP6) to show that acute social isolation potentiates the bulk calcium signal on first contact with a novel social stimulus, but not a novel object. We have reproduced these findings (n=19, p=0.028), and further show that responses to social stimuli are potentiated after both social isolation and food deprivation (n=11, p=0.002), while responses to food stimuli are potentiated only after food deprivation, but not social isolation (n=11, p=0.03). Using dual-site recordings, we find that baseline correlation between DRN and ventral tegmental area (VTA) DA calcium signal is low (Pearson's correlation coefficient, $r=0.05$), but increases significantly following introduction of a social stimulus ($r=0.24$, t-test p=0.007). We speculate that internal/motivational state can modulate the DRN DA response to salient stimuli in order to coordinate behavior and restore homeostatic balance.

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Poster

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PIIF
PNDRF
JFDP

Title: Neurotensin in the basolateral amygdala gate valence-specific plasticity underlying associative learning

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Abstract: Rewarding and threatening outcomes necessitate opposing behavioral responses. Previous work from our lab has shown that inputs to basolateral amygdala (BLA) neurons projecting to nucleus accumbens (NAc) and centromedial nucleus of the amygdala (CeM) undergo opposing synaptic changes upon acquisition of positive and negative associations, respectively. However, mechanisms underlying this selectively opposing regulation are unknown. Transcriptome profiling of BLA-NAc and BLA-CeM neurons revealed the neurotensin receptor 1 (NTSR1) gene as one of the most differentially expressed between the functionally opposing populations. We therefore hypothesize that the level of neuropeptide neurotensin (NT) present in BLA is a potential mechanism for selective modulation of positive associations in the BLA. Multiple lines of evidence support the absence of NT in the BLA as selectively enhancing reward learning. Infusion of NTSR1 antagonist into the BLA enhanced reward but not fear learning during associative tasks ($p=0.03$, NTSR1 antagonist $N=9$, control $N=9$). A NT bath preceding spike-timing dependent induction of long-term potentiation (LTP) reduced LTP onto BLA-NAc neurons but enhanced LTP onto BLA-CeM neurons ($p=0.02$, BLA-NAc ACSF $n=7$, NT $n=12$, $p=0.01$ BLA-CeM ACSF $n=8$, NT $n=12$). We then identified three sources of NT to BLA: the medial geniculate nucleus (MGN), the paraventricular thalamic nucleus (PVT), and the ventral hippocampus (vHPC). Each of these sources co-release glutamate onto BLA neurons. We therefore disrupted NT in each of these regions through the use of the CRISPR-Cas9 system to isolate the effect of NT. Ensuing behavior in associative learning tasks suggests that NT from the PVT has the largest and only significant effect on reward learning of the input regions ($p=0.03$, NT $N=15$, control $N=13$). Supporting this result, fiber photometry recordings of calcium transients in each region show that the largest change during associative learning occurs in the PVT. In conclusion, we have discovered that divergent BLA neural populations are differentially sensitive to NT, a neuropeptide whose action modulates BLA-mediated learning. Moreover, we identify multiple sources of NT to the BLA, and provide initial evidence of a circuit mechanism whereby NT-expressing neurons likely impact synaptic transmission onto BLA neurons during positive and negative associations.

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Poster

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Title: Closed-loop phase-locked electrical stimulation alters low-frequency coherence in a fear regulation circuit

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Abstract: Functional brain connectivity 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 safety memories. Clinical exploitation of this knowledge is limited by the lack of established paradigms to alter inter-area synchrony. In this work, we aimed to alter PFC-BLA oscillatory synchrony 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. The LFPs of IL and BLA were recorded for 5 minutes before the experiment to establish a baseline. We then monitored the IL theta-band (4-8 Hz) phase in real time for 30 minutes and delivered phase-locked single electrical pulses (100 μ A and 90 μ s pulse width) to BLA when IL phase was at 180°. We implemented a real-time phase estimation algorithm to ensure precise stimulation timing. Our stimulation control program also reduced variance in transmission delay by equalizing elapsed time between detection of the phase of interest and pulse delivery. We measured entrainment (coherence) of the low-frequency LFP between IL and BLA every 15 minutes from 0 to 90 minutes post-stimulation.

The phase-locking stimulation method achieved a mean error of 2.74° from the targeted 180° phase, with a circular error variance of 0.605 (on a scale of 0 to 1). Our method timed stimulation closer to the target phase than other published works, with a 5-20-fold improvement.

Our method also reduced the circular variance of stimulation phases relative to the best published comparable algorithm by 25%. The coherence between IL and BLA increased up to 8 standard deviations over baseline immediately post-stimulation. This increase could be observed within a single animal and day and is specific to the theta frequency band (4-8 Hz). The coherence enhancement was also long-lasting and could be observed up to 90 minutes post-stimulation with an averaged z-score of 1 over baseline.

We have demonstrated a closed-loop electrical stimulation technique to alter brain oscillatory synchrony. This may provide a new technique for neuroscientists to study brain networks. Future work will investigate how effectively closed-loop stimulation methods can alter anxiety-related behaviors, which would provide evidence for oscillatory synchrony as a key communicative mechanism and may eventually lead to more effective therapies for treatment-resistant varieties of psychiatric disorders.

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Poster

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Title: Effects of deep brain stimulation of ventral striatum in an operant set-shifting paradigm in rats

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Abstract: Cognitive flexibility is the ability to appropriately adjust one's behavior in response to environmental challenges. Deficits in cognitive flexibility are thought to be central to several psychiatric disorders, such as obsessive-compulsive disorder (OCD) and major depression (MDD). Recent evidence from our lab showed that cognitive flexibility in humans can be improved by deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VCVS), a frequent target for DBS treatment of OCD and MDD. Considering that the flexibility is poorly explored in animal models of those pathologies, and that the mechanisms underlying the beneficial effects of DBS remains not fully understood, here we: 1) explore if DBS can also improve flexibility in rodents submitted to an operant set-shifting paradigm; 2) try to identify

better targets/stimulation parameters to improve DBS technology in a way it can be translated back to clinics. For this, rats were implanted with electrodes aimed to a region analog to the human VCVS, the dorsal part of the VS. DBS (0, 100, 200 or 300 μ A) was delivered for 1 h prior to the set-shifting test and the different DBS intensities were administered on alternate days. DBS (300 μ A) significantly improved animals' reaction times (RT, -22 ms mean difference, $t = -2.34$, $p < 0.05$ for regression coefficient, $n = 7$), without increasing the number of errors ($t = 0.25$, $p > 0.05$). In addition, 300 μ A DBS effects were more pronounced when the electrodes were placed in more dorsal areas of the VS (RT, -38 ms, $t = -2.76$, $p < 0.05$), without affecting the error rate ($t = -1.62$, $p > 0.05$). Our data support that the stimulation of equivalent of the VCVS in animal models may enhance flexibility, with better effects obtained with higher stimulation at more dorsal targets. It is possible that the DBS effects observed here result from alterations in the pre-frontal cortex functioning. It is still to be tested if this effect occurs by the modulation of striatum/thalamus through efferent cortico-striatal projections, or by antidromically activating those same fibers and directly modulating PFC. Further experiments will explore additional targets and stimulation parameters that can lead to better DBS treatment effectiveness.

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Poster

075. Emotion: Neurocircuitry I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 075.25/YY9

Topic: G.03. Emotion

Support: NIH Grant 1UH3NS100548-01

Title: In search of biomarkers of obsessive-compulsive disorder: Combined cortical and striatal stimulation for re-regulating circuits of obsessive-compulsive disorder

Authors: ***M. BILGE**^{1,2}, M. J. BOGGESE^{1,2}, A. P. ROCKHILL^{1,2}, A. K. GOSAI^{1,2}, E. HAHN^{1,2}, C. CUSIN¹, T. DECKERSBACH^{1,2}, W. ZIV³, D. D. DOUGHERTY^{1,2}, A. S. WIDGE^{1,2,4}

¹Psychiatry, Mass Gen. Hospital/Harvard Med. Sch., Boston, MA; ²A. A. Martinos Ctr. for Biomed. Imaging, Boston, MA; ³Neurosurg., Mass Gen. Hosp., Boston, MA; ⁴MIT, Picower Inst. for Learning & Memory, Boston, MA

Abstract: One neural marker of Obsessive-Compulsive Disorder (OCD) is hyper-connectivity of Cortico-Striatal-Thalamo-Cortical (CSTC) loops. Deep brain stimulation (DBS) has shown initial promise for treating OCD, yet stimulation needs to be guided by biomarkers of CSTC hyperconnectivity and reliable clinical response. Recently, in one OCD patient we have begun

stimulating and recording from Ventral Capsule/Ventral Striatum (VC/VS; striatal) DBS target and the Supplementary Motor Area (SMA; cortical) using Medtronic's PC+S system. PC+S allows us to record task-free, automatically triggered local field potential (LFP) recordings from both striatal and cortical leads in regular time intervals. Preliminary data from striatal and cortical LFP recordings have demonstrated a decrease in striatal-cortical coherence for frequencies between 8 and 30 Hz with striatal stimulation. Further, we have observed striatal-cortical coherence increase at around 10 Hz as response to acute stimulation setting changes, in line with intra-operative recordings. The observed changes in striatal-cortical coherency could guide us in maximizing the clinical benefit of cortical stimulation. In addition to task-free biomarkers, we have recently started exploring task-based biomarkers. By using a response-inhibition task (i.e., Multiple Source Interference Task) and a separate task for fear re-learning (i.e., Fear Extinction) we are now tapping at prominent dimensions of OCD. Striatal LFPs and EEG during the performance of these tasks will allow us to evaluate whether task-free biomarkers are implicated also in task-directed cognitive and emotional functioning.

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Poster

075. Emotion: Neurocircuitry I

Location: SDCC Halls B-H

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Program #/Poster #: 075.26/YY10

Topic: G.03. Emotion

Support: NIH Grant RO1MH100536

Title: Sex differences in expression and distribution of small conductance calcium-activated potassium channels in the rat basolateral amygdala

Authors: ***B. L. AVONTS**¹, J. E. VANTREASE¹, J. H. URBAN², J. A. ROSENKRANZ¹
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Abstract: An estimated 31% of U.S. adults are diagnosed with an anxiety disorder in their lifetime with a prevalence twice as high in females. However, the neurobiological mechanisms contributing to this are poorly understood. The amygdala is hyperactive in patients with anxiety disorders and there are sex differences in the amygdala response to emotionally provoking stimuli. The basolateral amygdala (BLA) plays a role in fear and anxiety. BLA activity, in part, is controlled by small conductance calcium-activated potassium (SK) channels which mediate afterhyperpolarizations (AHPs) following action potentials. SK2 channels inhibit neuronal firing and overexpression of the SK2 isoform can protect against anxiety. Because we have shown that BLA neuronal activity is higher in female rats compared to males, we hypothesized that females will have less SK2 channel expression. Using quantitative PCR we found no sex differences in SK2 mRNA levels, however, we did find reduced SK2 protein expression in the BLA from female rats using Western blot analysis. This data suggests reduction of SK2 protein, but not mRNA, is responsible, in part, for the sex differences seen in BLA neuron activity of naïve rats. But the distribution of these proteins within the BLA remain unknown. Recently, we have found that there is a shift in neuronal activity over the estrous cycle with increased lateral (LAT) neuronal firing during diestrus but increased basal (BA) neuronal firing in proestrus. Therefore, we hypothesized that overall, females will have less SK2 expression throughout the BLA compared to males, as well as an increased expression of SK2 in the BA nuclei during diestrus and greater distribution of SK2 in the LAT nuclei during proestrus. Preliminary examination of SK2 immunoreactivity supports these hypotheses as SK2 expression was reduced in the BLA of female rats compared to males. Moreover, increased SK2 expression was observed in the BA nuclei compared to the LAT nuclei. Together these data suggest SK2 distribution across the BA and LAT nuclei may contribute to the sex differences observed in BLA activity. These results provide a mechanism for sex differences in the activity of the BLA and may be a target in the higher prevalence of anxiety disorders in females.

Disclosures: **B.L. Avonts:** None. **J.E. Vantrease:** None. **J.H. Urban:** None. **J.A. Rosenkranz:** None.

Poster

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Topic: G.03. Emotion

Support: China MOST 2012YQ03026005

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China NNSFC 91432114

China NNSFC 91632302

Title: Hypothalamic circuits for predation and evasion

Authors: *J. ZENG, Y. LI, J. ZHANG, C. YUE, W. ZHONG, Z. LIU, Q. FENG, M. LUO
Natl. Inst. of Biol. Sciences, Beijing, Beijing, China

Abstract: The interactions between predator and prey represent some of the most dramatic events in nature, and constitute a matter of life-and-death for both sides. The hypothalamus has been implicated in driving predation and evasion; however, the exact hypothalamic neural circuits underlying these behaviors remain poorly defined. Here, we demonstrate that inhibitory and excitatory projections from the mouse lateral hypothalamus (LH) to the periaqueductal gray (PAG) in the midbrain drive, respectively, predation and evasion. Using a dual-virus strategy, we found an increase in the activity of PAG-projecting LH neurons starting when starving mice began to hunt crickets. Activating these PAG-projecting LH neurons drove predatory attack. In patch-clamp recordings of brain slices, stimulating the axonal terminals from retrograde-labeled LH neurons evoked a mixture of GABAergic inhibitory currents and glutamatergic excitatory currents in PAG neurons, indicating that these PAG-projecting LH neurons can release the neurotransmitters GABA and/or glutamate. LH GABA neurons were activated during predation. Inhibition of LH GABA neurons suppressed cricket-hunting behavior. In a computer controlled food-chasing task, optogenetic inhibition of LH GABA neurons during the initiation stage prevented mice from chasing the moving food dish. However, inhibition applied immediately after pellet retrieval did not disrupt an animal's gnawing (putatively consummatory) behavior. Cell type-specific activation of LH GABA neurons drove predatory attack upon cricket, an artificial prey and intraspecific targets. Both cell type-specific and projection-specific stimulating of PAG-projecting LH GABA neurons drove strong predatory attack, and inhibiting of these cells reversibly blocked predation. In contrast, LH glutamate neurons were activated during evasion. Stimulating PAG-projecting LH glutamate neurons drove evasion, and inhibiting them impeded predictive evasion. Therefore, the seemingly opposite behaviors of predation and

evasion are tightly regulated by two dissociable modular command systems within a single neural projection from the LH to the PAG.

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Poster

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Topic: G.03. Emotion

Support: NIH Grant 1FI2GM119962-01

Title: A medial amygdala circuit predicts aggressive behavior

Authors: *J. NORDMAN¹, Z. LI²

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Abstract: Violence and aggression are serious concerns for modern society. While much has been learned about the neural mechanisms underlying aggression, the circuit level dynamics require further elucidation. Here we show that canonical members of the aggression circuit, the medial amygdala, ventromedial hypothalamus, and bed nucleus of the stria terminalis, form an important trisynaptic circuit that are essential for regulating select aggression features as well as being predictive of future attacks. Immunolabelling of brain sections from aggressive animals using cFos show an increase in activity in these three regions. Single cell recordings reveal a pathway specific correlation between firing rate, the onset of attacks, and attack duration. To determine if the onset and duration of aggression alters synaptic strength, we obtained in vivo electrophysiological recordings of spiking behavior and EPSPs from ventromedial hypothalamic and bed nucleus of the stria terminalis neurons, optogenetically evoked by their presynaptic partners, channelrhodopsin expressing medial amygdala neurons. We found alterations in neural activity during and after an aggressive episode, suggesting that the changes in firing rate and strength of EPSPs are the result of this trisynaptic circuit. Further, this data demonstrates that aggressive behavior can be delineated along pathway specific lines. These findings help elucidate the neural mechanisms underlying violent attack behavior and reveal future therapeutic targets in the treatment of aggression disorders.

Disclosures: J. Nordman: None. Z. Li: None.

Poster

075. Emotion: Neurocircuitry I

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Mary K. Chapman Charitable Trust

Title: Identification of the downstream partners of aggression promoting, peptidergic neurons

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Abstract: The neural circuits underlying the motivation for, or the likelihood of, performing a behavior have been more difficult to dissect than those underlying sensory and motor systems. The fruit fly, *Drosophila melanogaster*, is a powerful model for elucidating the neural basis of motivational behaviors such as aggression. We previously found a set of male specific neurons, called Tk-GAL4^{FruM+} neurons, that increase a fly's level of aggression upon activation. These neurons express the neuropeptide tachykinin that, along with one of its receptors, Takt86C, contribute to an increase in "aggression motivation" observed during Tk-GAL4^{FruM+} stimulation. We hypothesize that (1) a subset of downstream neurons are likely to express Takt86C, and that (2) these neurons must project at least to the vicinity of the pre-synaptic sites of Tk-GAL4^{FruM+} neurons and that (3) some subset of Takt86C expressing neurons will be important for aggressive motivation. We first expressed genetic markers for both the pre- and post-synaptic regions in the Tk-GAL4^{FruM+} neurons, and found that the pre-synaptic marker (synaptotagmin:GFP) is localized at a ring-shaped neural arbor in the superior medial protocerebrum. To visualize and manipulate Takt86C-expressing neurons, we created a LexA knock-in allele of Takt86C by using CRISPR/Cas-9-based genome editing technique. We found that some processes of Takt86C-expressing neurons overlap with a pre-synaptic site of the Tk-GAL4^{FruM+} neurons. Functional calcium imaging confirmed that Takt86C neurites in this region show Ca²⁺ response to Tk-GAL4^{FruM+} optogenetic activation. Furthermore, silencing of the Takt86C with temperature sensitive form of dynamin (shibire^{ts}) greatly reduced Tk-GAL4^{FruM+} activation-induced aggression. Therefore, the next question is to determine which subset of Takt86C neurons are important for aggression.

To do so, we found enhancer trap lines that label neurons with processes in the area of interest. Using a genetic strategy, we screened for aggressive behaviors while activating the intersection of these lines with the Takt86C knockin. We found a few lines that increased aggression. We are currently investigating the functional connection between these lines and the Tk-GAL4^{FruM+} neurons. Lines that are monosynaptically connected will be further characterized to determine

physiological properties and the role that the Tk receptor plays in aggression. Through these studies, we aim to characterize the physiological properties of the tachykininergic microcircuits that control aggression, and to better understand a neuronal mechanism that underlies the transformation from motivation to behavior.

Disclosures: **M.P. Wohl:** None. **K. Asahina:** None.

Poster

076. Emotion: Neurocircuitry II

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Topic: G.03. Emotion

Support: NINDS R01NS024760
NIMH R01MH101209
NIMH R01MH057414

Title: Inhibitory postsynaptic targets of pathway from anterior to subgenual cingulate

Authors: ***M. P. JOYCE**, H. BARBAS
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Abstract: Primate area 25 (A25) has weak connections with the dorsolateral prefrontal cortex (DLPFC), except for a moderate linkage with the frontal pole. The anterior cingulate area 32 (A32) may be a crucial conduit for information from lateral DLPFC areas to A25, as A32 is strongly connected with both. A32 is associated with many cognitive and affective functions, including attentional control. This indirect serial pathway, from the DLPFC to A32 and then to A25, may thus contribute to emotional regulation and the ability to shift attention flexibly among emotional domains, both positive and negative. We examined the postsynaptic targets of the pathway from A32 to A25 using functionally distinct inhibitory neuronal classes as distinguished by the calcium binding proteins (CBP) parvalbumin (PV), calbindin (CB), and calretinin (CR). This tripartite categorization is robustly used in primates because the three classes are non-overlapping in immunoreactivity and have distinct functional characteristics. The CBPs also label dendritic arbors, which makes them ideal for investigation as postsynaptic targets. We examined the appositional and postsynaptic targets of the pathway from A32 to A25 using meso and ultrastructural analyses via confocal and electron microscopy, respectively. Our results showed that while the majority of A32 axons targeted excitatory postsynaptic sites (~70%), as is common of corticocortical connections, inhibitory targets of A32 varied by laminar group, with a preference for CR neurons in all layers of A25. CR neurons in the upper layers of primate cortex have disinhibitory effects on pyramidal neurons by targeting other inhibitory neurons that populate the superficial layers. In the deep layers of A25, A32 also targeted a significant number

of PV postsynaptic targets. PV neurons are capable of strong inhibition due to their innervation of perisomatic elements of pyramidal neurons. The structural integrity of the pathway from A32 to A25 may be critical for healthy emotional function and shifts in innervation targets may affect cortical dynamics, attention to emotional domains, and modulation of deep layer output to autonomic structures.

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Poster

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Support: Wellcome Trust Investigator Award 108089/Z/15/Z to A.C.R.

MRC Doctoral Training Programme Studentship to L.A.

MRC Career Development Award RG62920 to H.F.C.

Title: Over-activation of primate subgenual anterior cingulate cortex induces anxiety, anhedonia and reductions in vagal tone

Authors: *L. ALEXANDER¹, P. L. R. GASKIN¹, S. J. SAWIAK², T. D. FRYER², Y. T. HONG², G. J. COCKCROFT¹, H. F. CLARKE¹, A. C. ROBERTS¹

¹Physiology, Develop. and Neurosci., ²Wolfson Brain Imaging Ctr., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Depression is a heterogenous syndrome with a variety of co-occurring symptoms including enhanced negative emotion, anhedonia and cardiovascular dysregulation. It is also highly co-morbid with anxiety. Indeed, resting state connectivity associated with anxiety and the symptom of anhedonia has revealed novel biotypes of depression (Drysdale et al., 2017; Nature Medicine 23:28-38). Whilst elevated activity within the subgenual anterior cingulate cortex (sgACC, including area 25) has been implicated in mood disorders - together with normalization of this activity following successful treatment - whether these activity changes are causally related to symptoms of depression and if so, to which symptoms, remains unknown. Here we combine targeted intracerebral microinfusions with cardiovascular and behavioral monitoring in marmoset monkeys to show that over-activation of primate sgACC/25 has profound effects on cardiovascular function, anhedonia and anxiety. At rest, over-activation of sgACC/25 causes extensive cardiovascular changes including elevating heart rate, lowering heart rate variability and reducing vagal tone. The same manipulation blunts specific arousal responses in appetitive situations (reducing both reward anticipation and motivation without affecting reward consumption) but elevates arousal responses in aversive situations (increasing intolerance of

uncertain threats and enhancing fear recall). Acute treatment with the antidepressant ketamine successfully reverses over-activation associated impairments in reward anticipation, but fails to ameliorate increased intolerance of an uncertain threat. Taken together, these results identify the major contribution of sgACC/25 over-activity to both symptoms of anxiety and anhedonia and their differential sensitivity to acute ketamine treatment. Current work using ^{18}F -FDG imaging is comparing the network-wide changes following sgACC/25 over-activation in both appetitive and aversive contexts, and the modulation of these brain networks by ketamine to exert its efficacious actions in specific symptom domains.

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Poster

076. Emotion: Neurocircuitry II

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Topic: G.03. Emotion

Support: NIMH R01 MH057414

Title: Complementary pathways from A25 and hippocampus to the amygdala in primates

Authors: *J. WANG¹, M. P. JOYCE¹, H. BARBAS²

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Abstract: Area 25 (A25), the hippocampus and amygdala are key nodes in limbic circuits with crucial roles in affective, cognitive and memory processes. Both A25 and the hippocampus send robust terminations to the amygdala, but knowledge about the organization of these pathways is limited in primates. We compared termination patterns of A25 and hippocampal pathways in the amygdala in rhesus monkeys. A25 preferentially targeted the dorsal part of the amygdala, including the medial nucleus, the magnocellular division of the basolateral nucleus (BL), and the central nucleus. Posterior A25 had denser terminations in the amygdala than anterior A25, especially in posterior levels of the amygdala. By contrast, hippocampal terminations were concentrated in the ventral part of the amygdala, including the parvicellular division of the BL and basomedial nuclei, the paralaminar basolateral (PLBL), and cortical nuclei. Stereologic analysis showed that BL and PLBL contained the highest proportion of hippocampal terminations in the amygdala. Hippocampal axon boutons were similar in size between BL and PLBL. Using confocal microscopy, we studied the relationship of hippocampal terminations with inhibitory neurons in BL and PLBL by labeling for the calcium binding proteins calbindin (CB), calretinin (CR) and parvalbumin (PV), which represent non-overlapping populations of inhibitory neurons in the primate amygdala. More hippocampal terminations were apposed on

CR+ and CB+ neurons in the amygdala than PV+ neurons, especially in PLBL. The hippocampus innervated both excitatory and specific inhibitory neurons in these areas, suggesting a complex modulatory role. Moreover, the major targets of hippocampus were the parvicellular division of BL and PLBL in the amygdala, which receive convergent inputs from other parts of the amygdala. As a whole, the amygdala received pathways from A25 and the hippocampus in mostly complementary sites, indicating that cognitive, affective and mnemonic information from these areas may work cooperatively to influence the activity in the entire amygdala.

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Poster

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Topic: G.03. Emotion

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Title: Relay of affective stimuli from amygdala to thalamus parallels sensory pathways

Authors: *C. TIMBIE^{1,3,2}, M. GARCIA-CABEZAS³, B. ZIKOPOULOS^{4,5}, H. BARBAS^{3,4}
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Neurosci. Laboratory, Dept. of Hlth. Sci., Boston Univ., Boston, MA

Abstract: The amygdala, the emotional sensor of the brain, is strongly connected with the posterior orbitofrontal cortex (pOFC), forming a pathway activated by reward learning. In addition, the amygdala innervates neurons in the mediodorsal thalamic nucleus (MD) that project to pOFC, forming a second, indirect route for the amygdala to influence the pOFC sector of the prefrontal cortex. The indirect pathway that connects the amygdala and pOFC through the thalamus may be similar to sensory pathways connecting peripheral receptors with sensory cortices through sensory relay thalamic nuclei. The indirect pathway is morphologically distinct from the direct pathway; amygdalar pathway terminals in MD are larger than those in the pOFC, and likely derive from separate neuronal populations in the amygdala (Timbie and Barbas, Society for Neuroscience, 2013; J Neurosci, 2015). The synaptic interactions and potential specializations of amygdalar terminals in MD have not yet been described in comparison to other thalamic afferents. We addressed this issue by labeling amygdalar axons in MD in rhesus monkeys and compared them with retinal axons terminating in the lateral geniculate nucleus (LGN). We studied axon terminations in MD and LGN using serial section electron microscopy

and analyzed pre- and post-synaptic elements by morphology. All amygdalar terminals in MD and retinal ganglion terminals in LGN contained multiple mitochondria, and were classed as round, large (RL) boutons. Amygdalar and retinal RL boutons contained excitatory type vesicles and formed several asymmetric (excitatory) synapses with dendrites of thalamocortical relay neurons and dendrites of inhibitory interneurons. In a significant proportion of these multi-synaptic arrangements, the inhibitory dendrites contained vesicles and formed symmetric synapses with the dendrite of the thalamocortical neuron. These novel findings reveal that amygdalar terminals in MD form synaptic triads, reminiscent of those found in sensory thalamic relay nuclei, like LGN. Our findings suggest that amygdalar inputs to MD can drive signals to cortex, ensuring efficient transmission of salient emotional information, akin to sensory thalamic relays.

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Poster

076. Emotion: Neurocircuitry II

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Program #/Poster #: 076.05/YY18

Topic: G.03. Emotion

Title: Social valuation requires interaction of prelimbic cortex and amygdala in rhesus macaques

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Abstract: Humans with bilateral ventromedial prefrontal cortex (vmPFC) damage, or bilateral amygdala damage, show deficits in social behavior. Similarly, experimental lesions in nonhuman primates that involve the anterior cingulate cortex (ACC), a subregion of vmPFC, or the amygdala result in changes in social behaviors including decreased social dominance, affiliative interactions, and social interest in other macaques. These findings suggest that a functional interaction between these two structures may play a role in guiding adaptive social behaviors. In the present study, we tested whether functional interaction between the prelimbic cortex (PL), a subregion of the ACC, and the amygdala (AMY) is necessary for social valuation (e.g., valuation of social stimuli relative to the incentive value of food). We compared monkeys with surgical disconnection of the PL and AMY (PLxAMY; $n=4$) to a group of unoperated controls ($n=5$) and monkeys with surgical disconnection of the premotor cortex and amygdala (PMxAMY; $n=2$). The PMxAMY group was not expected to show deficits in social behavior and therefore served as a surgical control group. Compared to control monkeys and the PMxAMY group, monkeys with surgical disconnection of the PL and AMY showed reduced latencies to reach for a reward in the presence of videos of conspecifics under different social contexts, indicating reduced

social valuation and/or reduced social interest. During the first session that the videos were presented, the reduced food-retrieval latencies were evident regardless of whether or not the social stimulus was threatening (e.g., video of a staring monkey), non-threatening (e.g., video of a small monkey), or affiliative (e.g., video of a monkey lip-smacking). Notably, the groups did not differ with respect to food-retrieval latency for neutral videos (e.g., a snowy field). We further sought to characterize the food-retrieval latency data by scoring the number of affiliative and aggressive or conflict-related behavioral responses for the videos. These data show that the prelimbic cortex and amygdala act as part of an integrated neural unit to guide adaptive social responses.

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Poster

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Topic: G.03. Emotion

Support: Werner Reichardt Centre for Neuroscience (H.C.E.)
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Title: Multimodal characterization of the functional and anatomical connectivity of the anterior insular cortex in the macaque monkey

Authors: *J. SMUDA^{1,2,3}, C. KLEIN¹, Y. MURAYAMA¹, N. LOGOTHETIS^{1,4}, H. EVRARD^{2,5}

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Abstract: We examined the dynamic functional connectivity of the von Economo neuron (VEN) area of the anterior insula cortex (AIC) using two-shot echo-planar functional magnetic resonance imaging with direct electrical stimulation (DES-fMRI), seed-based connectivity analysis (SBCA), and local field potential recordings (NET-fMRI) in the anesthetized macaque monkey. The electrical stimulation (n=3) of the left or right VEN area activated several distinct subcortical limbic nuclei (e.g. amygdala, midline thalamic nucleus [MTN]) and high-order cortical areas (e.g. superior temporal sulcus, extrastriate visual areas). Both the left and the right stimulation produced a rather lateralized activation pattern, with the activation elicited from one side roughly mirroring the activation obtained from the other side. Nevertheless, stimulation of

the left VEN area elicited a consistently more intense and broader bilateral activation. The correlation patterns obtained with a SBCA of the same data set, using the left and right VEN area as seeds, confirmed the activation patterns elicited by the electrical stimulation. Conversely, SBCA using spontaneous data sets, collected in the same animals without electrical stimulation, revealed not only a correlation between both VEN areas but also a broader bilateral correlation pattern that remained identical regardless of the seeded side. Whereas many limbic and cortical activations produced by the electrical stimulations were matched by a correlation with the spontaneous activity of the VEN areas, the MTN was neither correlated nor anticorrelated with the spontaneous activity. Finally, in the NET-fMRI with the same spontaneous functional scans, the occurrence of oscillatory events (e.g. alpha, theta, gamma) in the left or right VEN area triggered varying patterns of activity that differed from the electrical stimulation patterns while being nonetheless markedly asymmetric. Events from the left or right VEN area often correlated with respectively massive activation or deactivation patterns. The present study reveals that small individual regions of the brain can simultaneously display a broad diversity of functional connectivity patterns. The asymmetric activity patterns associated with the left and right VEN areas corroborate prior evidence for a left-right functional asymmetry in the AIC (Craig, 2005, Trends Cogn Sci). The spatially restricted or broad activation of limbic and high-order regions from the right and left VEN areas, respectively, might underlie the asymmetric role of the AIC in monitoring internal bodily states during cognitive processes, including subjective perceptual awareness.

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Poster

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Topic: G.03. Emotion

Support: Werner Reichardt Center for Integrative Neuroscience
Max Planck Institute for Biological Cybernetics
International Max Planck Research School

Title: fMRI and electrophysiological mapping of sensory afferent activity in the macaque insular cortex

Authors: *R. E. HARTIG^{1,2,3}, A. E. VEDOVELI^{1,2,3}, N. LOGOTHETIS^{2,4}, H. EVRARD^{1,2}

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Abstract: We examined the topographical organization of interoception in the dorsal fundus of the insula using fMRI, electrophysiological recordings and tract-tracing in anesthetized macaque monkeys. The fMRI experiments (n=12) examined the insular responses to graded cooling and heating of the hand and foot, to sweet, salty and sour taste stimuli, to rectal distention (RD) and to transcutaneous electrical stimulation of the auricular vagus nerve branch. Cutaneous thermal stimuli elicited activations in the posterior area of the dorsal fundus of the insula (Idfp), while activations related to gustatory, vagal and RD stimuli were localized more anteriorly, either in the anterior area of the dorsal fundus (Idfa) or, in the case of RD, in the lateral area of the agranular insula (Ial). Electrophysiological recordings (n=4) confirmed this overall topography. Recordings in Idfp revealed a somatotopic organization in which the foot, hand, and face were represented from posterior to anterior. Neurons in Idfp responded either to noxious heat, pinch and cold (HPC cells), or were nociceptive-specific with responses to only noxious cold or pinch (NS cells). Recording in the posterior half of Idfa revealed an extensive multi-sensory representation of the orofacial cavity including taste. Recording in the anterior half of Idfa revealed spontaneous rhythmic activities potentially correlated with visceral processes (e.g. heart rate, respiration). Tracer injections in recorded sites in Idfa or in Idfp confirmed prior evidence for specific thalamocortical projections from the basal and posterior parts of the ventral medial nucleus of the thalamus (VMb and VMpo), respectively (Craig, 2002, Nat Rev Neurosci, 3:655-66). The present study supports the idea that the dorsal fundus of the primate insula represents interoception in a manner that preserves the spino-cranial topography and the encoding of distinct interoceptive modalities (e.g. HPC and NS) along distinct labeled-lines throughout the neuraxis. This refined representation of internal bodily signals likely plays a crucial role in the homeostatically efficient shaping of cognitive processes by interoception, and provides the basis for the evolutionary emergence of embodied subjective feelings in the human anterior insula.

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Poster

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Title: Multiple areal distribution of the von Economo and fork neurons in the human anterior insular cortex

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Abstract: We analyzed the areal distribution of von Economo (VEN) and fork (FN) neurons in the human anterior insular cortex (AIC). The AIC, including the frontoinsula (FI), from eight freshly-fixed human brains (3 pairs of left and right insulae, and 5 single left or right insulae) were cut in the coronal plane at a 50-micron thickness. The sections were stained with cresyl violet to reveal all neuronal cell bodies and the proximal portion of their dendrites (Nissl stain), with silver nitrate to reveal myelinated fibers (Gallyas stain), or with an anti-parvalbumin antibody to reveal local interneurons. All stained sections were digitized with a 0.5-micron in plane resolution and 1-micron vertical stack using a scanning microscope. The distribution of the VEN and FN was charted using high-magnification examination of the Nissl slides. The AIC was parcellated using low-magnification examination of all three sets of slides with pre-established multi-architectonic criteria (Evrard et al., J Comp Neurol 2014 522:64-97). The VEN and FN were co-mingled within a rather vast region (or ‘VEN domain’) inside the ventral agranular region of AIC, with no apparent extension in the dorsal AIC or the dysgranular and granular insula. The VEN domain was delimited by a rather abrupt reduction of the numbers of both neurons. A comparison of the localization of the VEN domain with the architectonic parcellation of the AIC revealed (1) that its overall outer limit optimally overlapped with sharp architectonic boundaries, and (2) that it was further subdivided into at least three distinct architectonic areas (or ‘VEN areas’), rather than being homogeneous. While these three areas consistently occurred, their exact topology differed between the left and right hemispheres. Our prior examination of the macaque AIC revealed a complete overlap of the delimitation of a VEN/FN cluster with architectonic boundaries; however, this cluster formed one unique architectonic area, rather than being divided into several areas (Horn FM and Evrard HC, in preparation). The highly consistent overlap of the VEN distribution and architectonic boundaries (or “elemental localization”) in humans and monkeys indicates the existence of a robust selective pressure on the development of the AIC throughout evolution. The multiplication of the number of VEN areas likely correlates with the disproportionately faster growth of the AIC, including in particular FI, in humans compared to other primate species (Bauernfeind et al., J Hum Evol 2013 64:263-79). This multiplication might underlie the possible evolutionary emergence of the subjective awareness of feelings in the human AIC (Craig, Nat Rev Neurosci 2009 10:59-70).

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Poster

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Title: Stimulation induced facilitation and depression of neural activity in human and non-human primate cortex

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Abstract: Electrical neuromodulation is employed to treat an increasing number of neuropsychiatric disorders, yet knowledge of the relationship between stimulation parameters and neural response is sparse. We examined the relationship between evoked neural responses, pulse frequency, and current amplitude during trains of 10-400 Hz stimulation in non-human primates (NHP, N=4) and epilepsy patients (N=20). Targeting subcortical and cortical regions, we found: 1) neural responses vary linearly with current but nonlinearly with frequency; 2) specific combinations of parameters induce either the largest response or the fastest response time; and 3) homologous brain regions respond to stimulation with characteristic evoked potential waveforms which map to stimulation frequency. To better understand neuronal network state during these evoked responses, we introduced a single pulse of stimulation at different time points following stimulation trains (human, N=3; NHP, N=2). The cortico-cortical evoked potentials (CCEPs) from single pulse stimulation has multiple phases in the waveform and those phases are differentially modified based on both the frequency of the preceding train and the timing relative to completion of the train. In high preceding frequencies and longer time delays, this modification enhanced CCEPs and, with short time delays but, again, with high preceding frequencies, the CCEPs were depressed. These results provide a framework for the principled selection of stimulation timing and parameters to both achieve maximal therapeutic benefit and improve our understanding of how cortical activity is altered with neural stimulation.

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Topic: G.03. Emotion

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Title: Decoding of cognitive flexibility state using cingulate and pre-frontal cortical local field potentials during the performance of a multi-source interference task

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Abstract: A significant challenge in neuroscience is to identify underlying cognitive processes inaccessible to direct measurement, such as cognitive flexibility. Such cognitive processes can be represented as hidden states estimated through brain activity and/or behavioral responses. Cognitive Flexibility is the ability to rapidly shift one's attention and behavioral strategy in response to changes in the environment and is often compromised in a wide spectrum of psychiatric disorders such as mood and anxiety disorders. In this work, we used a state space framework to estimate a hidden cognitive flexibility state using behavior and neural data. Human participants consisted of eight patients with long-standing pharmaco-resistant complex partial seizures who voluntarily participated after fully informed consent. Participants performed a multi-source interference task (MSIT) with simultaneous recordings of reaction time (RT) and local field potential (LFP) from cortical and subcortical brain structures. The RT recorded for each trial of MSIT conveys the most relevant information about the participants' behavior and underlying cognitive flexibility. We used a state space modeling framework to first estimate a hidden baseline cognitive flexibility state from RT. We then estimated an encoder model relating the cognitive state to neural features extracted from prefrontal cortical LFPs. These features consisted of spectral power of the LFP in theta (4-8 Hz), alpha (8-15 Hz) and high gamma (65-200 Hz) bands over a time interval of 2 seconds aligned with image onset. Finally, using the encoder model, we determined a neural decoder to predict the cognitive flexibility state from a subset of neural features. We found that we could use 8-15 neural features to reliably decode the cognitive flexibility state. The mean decoded state using neural features was within 95 percentile confidence interval of the behavior (RT) decoded state 90 % of the trials on an average. Furthermore, the mean decoded cognitive states using neural features and behavior had an average correlation of 0.6. The root mean squared error between these decoded states was 10% of the total range of these cognitive states. In this work, we show that using both behavior and neural features recorded during the performance of a cognitive task, we can decode an underlying cognitive flexibility state. This framework can be used to design closed loop electrical stimulation to improve cognitive flexibility in patients with mood and anxiety disorders. The encoder model can also be used to identify neural features that encode a specific cognitive state.

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Poster

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Title: Stress-sensitive cortisol awakening response regulates emotional learning via altering amygdala-hippocampal prefrontal circuits

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Abstract: Dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis system, a central stress response system, has been linked to various affective disorders, suggesting that HPA-axis system plays a critical role in emotional processing. Cortisol awakening response (CAR), a physiological phenomenon in which cortisol level increases rapidly and reaches to peak around 30 minutes after awakening, is considered as a reliable index of HPA-axis activity. However, little is known about how CAR modulates human emotion processing and the underlying neurobiological mechanisms. Using event-related fMRI with concurrent skin conductance recording (SCR), we investigated how CAR affects human emotional learning and its related brain circuitry. We observed the formation of discriminative learning for danger and safety cues, with higher SCR in danger than safety cue in general. Critically, we observed that participants with low-CAR, as relative to high-CAR, showed lower SCRs for both danger and safety learning, which may indicate that subjects with low CAR had less phasic responsiveness to both danger and safety signals. On neuroimaging level, we observed a significant interaction effect between Group (High- vs. Low-CAR) and Learning (Early vs. Late) phase in emotional perception and regulation systems, including the bilateral amygdala, hippocampus, and lateral prefrontal cortex. That is, participants with high CAR showed an increase of emotional reactivity during the early to late phase of emotional learning, while low-CAR group showed an opposite

pattern. Further analysis of trial-by-trial multivoxel pattern similarity over learning revealed a gradually increasing learning curve in high-CAR group against a rather flatten curve in low-CAR group in the amygdala. Interestingly, we also observed significant interaction effects on functional coupling of the amygdala and hippocampus with the orbital frontal cortex (OFC), with reduced functional connectivity in low-CAR group from the early phase to late phase during emotional learning. This may reflect a reduce down-regulation of the OFC over the amygdala and hippocampal systems. Our findings demonstrate that CAR plays a critical role in regulating emotional learning through acting on functional coordination of the amygdala, hippocampal and prefrontal circuits involved in emotional perception and regulation.

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Poster

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Title: Neuroimaging multi-modality visualization and analysis tool

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Abstract: The visualization and exploration of neuroimaging data are important for the analysis of anatomical and functional images and statistical parametric maps. While two-dimensional orthogonal views of neuroimaging data are used to display activity and statistical analysis, real three-dimensional (3D) depictions are helpful for showing the spatial distribution of a functional network, as well as its temporal evolution. For our best knowledge, currently, there is no neuroimaging 3D tool which can visualize EEG, MEG, fMRI and invasive electrodes (ECOG, depth electrodes, DBS, etc.) in the same space. Here we present the multi-modality visualization tool (MMVT). The tool was built for researchers who wish to have a better understanding of their neuroimaging anatomical and functional data. The true power of the tool is by visualizing

and analyzing data from multi-modalities. In addition to the 3D visualization, a slicer viewer was implemented, which gives the user the benefit of both 3D and 2D worlds. A full translation is supported between the two representation, even when the 3D brain is inflated, or even being transformed to a full flap map. The users can process their raw data using the tool, or import existing results, where most of the formats are supported.

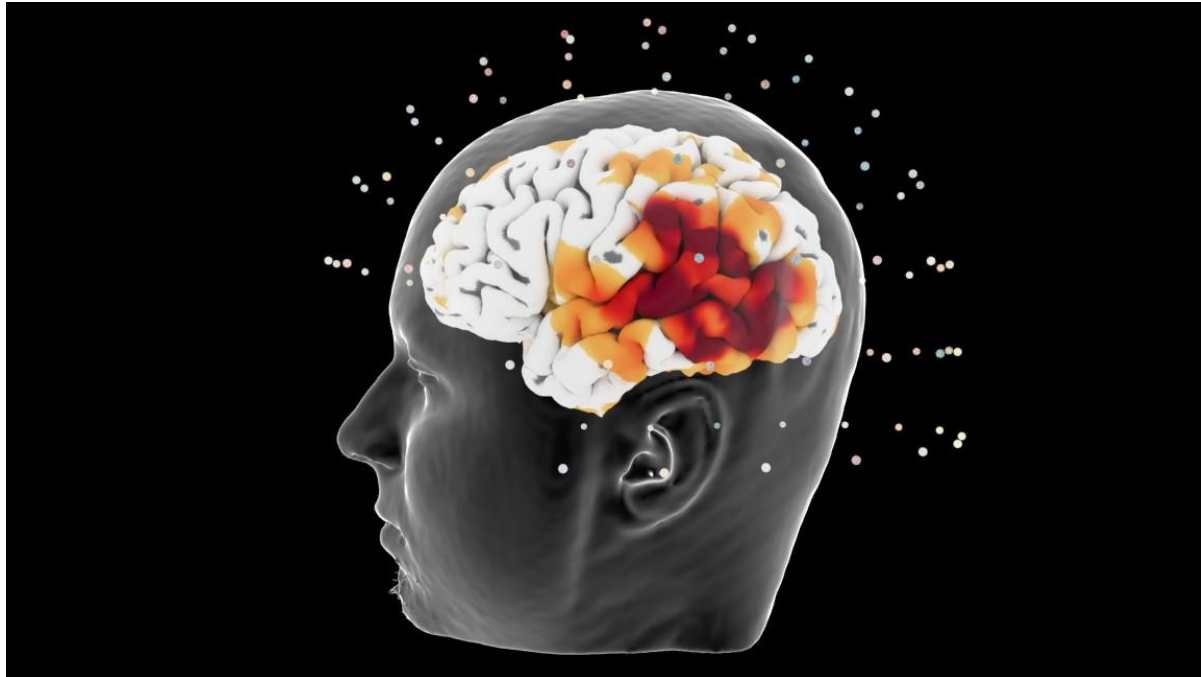


Figure1: MEG sensors and source (dSPM) evoked response

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Poster

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Topic: G.03. Emotion

Support: DARPA Cooperative Agreement Number W911NF-14-2-0045

Title: Closed-loop intracranial stimulation system for humans

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Abstract: Closed-loop brain stimulation is a promising therapeutic solution and research tool that could achieve better therapeutic results than periodic stimulation and help understand underlying mechanisms. However, current human protocols rely on open-loop stimulation, likely due to technical challenges to close the loop. We developed a closed-loop stimulation system based on real-time neural features calculation. Intracranial electrical brain signals are acquired, bipolarized, band pass filtered, and features (power or coherence) continuously computed. If features are above (below) threshold for certain duration, stimulation is triggered. Thresholds are updated periodically, based on triggers, or fixed and modified on real-time. Stimulation could occur following detection, after delay, or at trigger. Random stimulation, which percentage of detections produce stimulation, and safety refractory periods can be configured. We also incorporated model based detection to stimulate following decoded cognitive state. In this mode, features are computed per trial, averaged over time epochs, and a neural encoder/decoder model estimates a hidden state. If decoded state exceeds threshold, stimulation occurs on following trial. To ensure fixed processing times, it runs on a dedicated Simulink Real-Time computer with a separate GUI for configuration and real-time visualization. It runs in parallel to clinical and research systems. Replay of previously acquired datasets allows feature selection and model training. In four human participants, patients with pharmaco-resistant complex partial seizures implanted for clinical reasons who voluntarily participated after fully informed consent, we tested our closed-loop invasive stimulation system during cognitive tasks (task1: anterior cingulate to amygdala theta coherence, stimulation at following trial, N=1; task 2: prefrontal high-gamma power, N=1), sleep (spindle detection, N=1) and epileptic spikes detection (unfiltered power, nearby channel real-time stimulation, N=2). We performed multi-day experiments on two non-human primates (NHPs) during sleep (cingulate or prefrontal cortex stimulation, N=2) and attention (gamma power and theta coherence, N=1). In all cases, clear evoked responses (ERP) were observed after stimulation. Comparing detected vs. random stimulation resulted on a clear difference of feature values both on averaged and single trial analysis. Our system successfully triggers stimulation based on real-time detection and decoding of brain signals, providing a flexible platform for closed-loop intracranial experiments.

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Poster

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Topic: G.03. Emotion

Support: W911NF-14-2-0043, DARPA

Title: Closed-loop deep brain stimulation for chronic pain

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Abstract: Deep brain stimulation (DBS) for refractory pain disorders showed early promise but demonstration of long-term efficacy is lacking. Current DBS devices provide “open-loop” continuous stimulation and thus are prone to loss of effect owing to nervous system adaptation and a failure to accommodate natural fluctuations in chronic pain states. DBS could be significantly improved if neural biomarkers for relevant disease states could be used as feedback signals in “closed-loop” DBS algorithms that would selectively provide stimulation when it is needed. We present new data from the first clinical trial using closed-loop DBS for neuropathic pain. First, we discuss candidate neural biomarkers of elevated spontaneous pain states identified with local field potential recordings in the Anterior Cingulate and Orbitofrontal Cortex from human patients. These data are compared with biomarkers of experimental (acute) pain states. We then present preliminary closed-loop algorithms for personalized analgesic brain stimulation. In patients with post-stroke pain and phantom limb syndrome we describe early outcomes of personalized stimulation and outline a framework for a sham-controlled clinical trial.

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Poster

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Title: Intrinsic connectivity network activation during interoceptive and exteroceptive negative emotion processing - A comparative fMRI study

Authors: *B. JARRAHI, S. MACKEY

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Abstract: Interoception refers to the sensing and perception of the physiological condition of the body arising from the afferent (sensory) nerves such as those originating from the internal organs (e.g., bladder). Considered as a homeostatic emotion, interoception is associated with the endogenous homeostasis and underlies affective states. However, it is unclear how the neural system supporting interoception compares to the one underlying the processing of exteroceptive emotion. The aim of this comparative study was to elucidate the common and disparate neural networks underlying these two systems. Participants were 31 healthy volunteers (6 males, age range 20 - 39 years) with no current mental or urological disorders as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), and urodynamic measurements, respectively. After providing IRB-approved consent forms, participants were divided into two groups: the interoception group (n = 13, 31.7 ± 8.4 years) underwent viscerosensory stimulation task that consists of the controlled filling and emptying of the bladder in a block design, while the exteroceptive emotion group (n = 18, 29.7 ± 9.6 years) were scanned during the emotion processing task comprised of a block design presentation of emotionally salient stimuli from the IAPS database and the Ekman & Friesen's Pictures of Facial Affect series. Only negative salient stimuli were used since bladder interoception is often associated with negative emotion such as fear. Imaging data were acquired using a Philips Achieva 3T scanner, and preprocessed with SPM12. High-dimensional independent component analysis was performed using the infomax algorithm in GIFT. Results reveal that interoception activates the striatal salience network (striatum, insula, and thalamus), self-referential network (medial prefrontal and anterior cingulate cortices), frontoparietal central executive network, and limbic associated areas including amygdalohippocampal regions. The exteroceptive emotion engages a core network whose nodes comprised the ventromedial and orbitofrontal cortices, anterior cingulate, insula, amygdala, parahippocampal gyri, and thalamus. Two other networks including the frontoparietal central executive network, and the frontocingulate cognitive control network are also activated by exteroceptive emotion. These results provide preliminary evidence that the core exteroceptive negative emotion processing system of the brain has a considerable overlap with the key components of the interoceptive processing. Future studies are expected to shed more light on the neural underpinnings of emotion processing in human.

Disclosures: S. Mackey: None.

Poster

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NIMH R01 MH070539

Title: Gray matter correlates of emotional intelligence in incarcerated adult offenders

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Abstract: Emotional intelligence (EI) is form of social intelligence that is important for navigating one's social environment. Deficits in these abilities have been associated with a host of negative outcomes including anxiety, substance use, aggression, and psychopathic traits. Understanding the neural correlates of these abilities will provide us with a deeper understanding of the construct of emotional intelligence. Here, we extend current literature that suggests that EI is correlated with gray matter volume (GMV) and concentration (GMC) in limbic regions (e.g. insula, ventromedial prefrontal cortex, anterior cingulate, and cerebellum) in healthy samples, by using voxel-based morphometry (VBM) to assess the relationship between gray matter and EI in a sample of incarcerated adult males (n = 247). Emotional intelligence in our sample was positively correlated with GMV in the cerebellum and anterior cingulate cortex. Understanding neural correlates of EI in clinical samples, such as this one, is crucial in developing a more complete understanding of the construct of emotional intelligence. Furthermore, due to the increased incidence of negative outcomes related to EI in incarcerated populations, studies such as this may aid in determine whether it may be a viable target for interventions in this population.

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Topic: G.03. Emotion

Title: Inter-regional phase-amplitude coupling in cognitive reappraisal-based emotion regulation

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Abstract: Emotions play an integral role in daily life, often through their interactions with cognitive and behavioral processes. The broad impact of perceived emotions makes their effective regulation a key point of interest in cognitive research, though it is not easy to study in the same timescale as cortical activity and adaptation. In this experiment, a spatiotemporally-specific EEG-fMRI algorithm was used to identify the dynamic regional activity that underlies

emotion regulation when performed through cognitive reappraisal. 20 young-adult subjects were recruited as a part of this experiment, from which 3 were rejected due to poor data quality. Anatomical MRI data was collected from subjects who from whom simultaneous EEG and fMRI data was collected during an emotion regulation task. The experimental paradigm consisted of 4x 30-trial sessions (120 total trials), with each trial comprised of a 4-second cue period, a 2-second blank screen, and a 4-second exposure to the stimulus image, and 2 seconds of rest. Cues consisted of the words “watch” or “decrease”, which respectively informed the subject to either passively observe the stimulus or perform reappraisal, and stimuli consisted of neutral and negative-evocative images. The “decrease” cue was only used with negative images, leading to 3 conditions: Neutral (Neu), Negative (Neg), and Negative Emotion-Regulation (NER). The DBTN algorithm was the used to provide accurate estimates of cortical current from each region of interest identified by fMRI data. Inter-regional Phase Amplitude coupling was then calculated in 200 ms windows, with subsequent corrections for False Discovery Rate and window-based significance calculated through the Empirical Browns method. Modular interactions that were consistent across time points were identified for each band. Consistent couplings in the theta band showed broad networks of activity. The Neu and NER conditions showed largely symmetrical interaction networks, while the Neg condition eliciting a more lateralized response, in which couplings between the VLPFC/insula and retrosplenial cortices only appeared in the right hemisphere. Consistent couplings in the alpha band were most prevalent in the Neg condition and included the PPC, retrosplenial cortex, and ACC, with a lateral interactions in the VLPFC and Insula. The NER condition led to bilateral coupling interactions within the VLPFC, Insula, ACC and Retrosplenial cortex, with the Neu condition yielding a single constant coupling between the left PPC and ACC. Results show variable networks of coupling interactions between the salience and emotion networks, with the PPC and retrosplenial cortex interacting in both.

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Poster

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Title: Intrinsic functional connectivity in emotion regulation network is altered in emotional laborers

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Abstract: Emotional labor is considered as a kind of emotion regulation process, which includes managing one's emotion and emotional expressions to fulfill other people's expectations. Although several studies have described psychological characteristics of emotional laborers, little is known about the neurobiological consequences of emotional labor. In this study, we investigated whether patterns of intrinsic functional connectivity can differentiate between emotional laborers and healthy controls and which networks are the most crucial features that distinguish the two groups. Twenty-one emotional laborers and twenty-nine healthy controls participated in the study, and we collected 10 minutes of resting-state functional MRI data from each participant. To test whether we could classify two groups with patterns of resting-state functional connectivity, we first extracted each participant's BOLD time-series from each brain region and calculated the correlation coefficient for each pair of brain regions. These whole-brain functional connectivity matrices were then used for pattern classification analysis. Using a linear support vector machine classifier (SVM) and leave-one-out cross-validation (LOOCV), we found that the two groups could be successfully classified with extremely high accuracy on the basis of individuals' connectivity patterns. To further characterize the network structure of connectivity features used for classification, we calculated degree and betweenness centrality of each node with included edges. This analysis revealed that several prefrontal nodes, including ventrolateral prefrontal cortex (VLPFC) and ventromedial prefrontal cortex (VMPFC), showed greater degree and betweenness centrality than other nodes. Given that these prefrontal regions have been found to play an important role in emotion regulation, our results support the possibility that neural characteristics specific to the emotional labor group might be explained by alteration of neural connections in emotion regulation networks. Taken together, these findings suggest that intrinsic connectivity pattern can be useful in exploring the neurobiological changes associated with persistent work experiences.

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Poster

076. Emotion: Neurocircuitry II

Location: SDCC Halls B-H

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Title: Anxiety in irritable bowel syndrome is associated with increased inhibitory neurotransmitter concentrations and reduced functional connectivity of medial prefrontal cortex

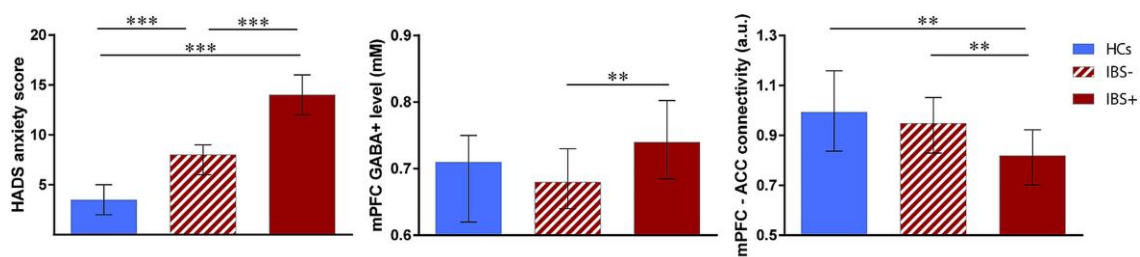
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Abstract: Altered neural mechanisms are increasingly acknowledged in the pathophysiology of irritable bowel syndrome (IBS), a disorder of brain-gut communication highly comorbid with anxiety and depression. As a key hub in corticolimbic inhibitory control with frequently reported functional alterations in IBS, the medial prefrontal cortex (mPFC) may play a crucial role in disturbed emotion regulation in IBS. However, aberrant mPFC excitatory and inhibitory neurotransmission potentially contributing to dysfunctional corticolimbic inhibitory control and to symptoms of anxiety and depression in IBS remains unknown.

Using quantitative magnetic resonance spectroscopy (qMRS), we compared mPFC glutamate+glutamine (Glx) and γ -aminobutyric acid (GABA+) concentrations in 64 women with IBS and 32 age-matched female healthy controls (HCs) and investigated their association with psychological symptoms in correlational and subgroup analyses. Applying resting-state functional magnetic resonance imaging (rs-fMRI), we explored whether altered neurotransmitter concentrations were paralleled by aberrant mPFC resting-state functional connectivity (FC). Generally, patients with IBS did not differ from HCs with respect to GABA+ or Glx levels in mPFC. Increased symptoms of anxiety were positively associated with mPFC GABA+ concentrations in IBS, whereas Glx levels were not correlated with psychological or gastrointestinal symptoms. Subgroup comparisons of patients with high or low severity of anxiety symptoms and HCs (Fig.1A) revealed increased GABA+ in patients with high anxiety symptom severity (Fig. 1B), paralleled by lower FC of mPFC with adjacent anterior cingulate cortex (ACC; Fig. 1C), a crucial region of emotion modulation.

Our multimodal findings provide novel evidence that alterations in prefrontal inhibitory neurotransmission and resting-state FC may be linked to anxiety in IBS as a model condition for disturbed brain-gut communication.



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Poster

077. Emotion: Fear, Anxiety, and Pain I

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 077.01/ZZ9

Topic: G.03. Emotion

Support: Medical College of Wisconsin Center for Imaging Research Daniel M. Soref Grant

Title: High resolution resting state functional connectivity in anxiety

Authors: *C. N. WEIS, A. A. HUGGINS, K. P. BENNETT, E. A. PARISI, C. L. LARSON
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Abstract: Anxiety is a common and chronic disorder that affects nearly a third of U.S. young adults. Research into the neurocircuitry underlying anxiety has implicated the bed nucleus of the stria terminalis (BNST), a small nucleus in the ventromedial forebrain, as a critical region that mediates symptoms. Behavioral studies have shown the BNST is most responsive in states of anxiety elicited by unpredictable threat, and maintains responsivity during the full period of threat anticipation. In addition, the BNST tracks the temporal and spatial proximity of threat, suggesting it is hypervigilant to potential threat. Structural and functional connectivity studies in rodents, nonhuman primates, and humans have consistently shown the BNST is connected with limbic structures, the basal ganglia, thalamus, paracingulate gyrus, and prefrontal cortices. Together these responsivity and connectivity findings allude to the BNST's role in anticipating and coordinating responses to unpredictable threat. If these anticipatory responses are unregulated, anxiety symptoms may result. While there is clear evidence for the BNST's role in anxiety, most of the work done thus far has been in non-human animals. The human BNST is less well understood due to its small size and difficulty measuring its activity using 3-Tesla MRI. Therefore, the current study utilized high resolution 7-Tesla MRI to characterize the functional connectivity of the BNST as it relates to trait anxiety and intolerance of uncertainty. A sample of 32 neurologically healthy undergraduate participants ($M_{age}=21.96$, $SD_{age}=3.36$) underwent structural and resting state functional MRI scans as well as completed the State-Trait Anxiety Inventory (STAI) and Intolerance of Uncertainty Scale (IUS). Whole brain voxel-wise analyses show greater trait anxiety is related to decreased functional connectivity of the BNST with the insula, basal ganglia, anterior cingulate cortex, and thalamus. In addition, greater intolerance of uncertainty is related to decreased functional connectivity of the BNST with the insula, basal ganglia structures, and parietal and temporal cortices. These results indicate potentially impaired

connectivity of the BNST with critical limbic and basal ganglia structures may contribute to greater anxiety.

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Poster

077. Emotion: Fear, Anxiety, and Pain I

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Topic: G.03. Emotion

Support: National Institute of Justice Grant 2017-R2-CX-0033

Title: Perceived stress and behavioral pattern separation in law enforcement officers

Authors: *D. W. GRUPE, R. J. DAVIDSON

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Abstract: Background. The hippocampal-dependent process of pattern separation allows for the differentiation of highly similar items in memory, and deficient pattern separation has been theoretically implicated in the pathology of posttraumatic stress disorder (PTSD). Here, we tested the novel hypotheses that a behavioral index of pattern separation would be associated with elevated perceived stress and PTSD symptoms in a group of law enforcement officers (LEOs). **Methods.** We recruited 60 participants as part of a randomized controlled trial of mindfulness training in LEOs. At baseline, participants completed the mnemonic similarity task (Stark et al., 2013), in which they classified a stream of common objects as either new (“foils”), old (“targets”), or similar (“lures”) to previous items. We calculated two memory indices: recognition memory, $P(\text{old} | \text{target} - \text{old} | \text{foil})$, and lure discrimination index (LDI), $P(\text{similar} | \text{lure} - \text{similar} | \text{foil})$, a behavioral index of pattern separation. Participants completed the Police Stress Questionnaire (PSQ), an occupationally-specific measure of perceived stress with separate organizational and operational stress scales, and the PTSD Checklist for DSM-V (PCL-5). We used correlational and regression analyses to relate the two behavioral indices to 1) perceived organizational and operational stress, and 2) PTSD symptoms. We hypothesized that LDI scores, but not recognition memory, would be negatively correlated with perceived work stress and PTSD symptoms, particularly hyperarousal symptoms that are theoretically related to overgeneralization. **Results.** Neither LDI scores nor recognition memory were related to total PSQ scores. However, a simultaneous regression analysis revealed opposite relationships for the organizational/operational PSQ scales with LDI. As predicted, elevated operational stress was correlated with lower LDI scores ($t(55) = -2.31, p < 0.05$), but elevated organizational stress was unexpectedly correlated with *higher* LDI scores ($t(55) = 2.93, p < 0.005$). PCL-5 total and

hyperarousal symptoms were unrelated to LDI, and recognition memory was not related to PSQ or PCL-5 scores (all $r_s < 0.1$). **Discussion.** A behavioral index of pattern separation showed distinct relationships with perceived organizational and operational stress in LEOs but was unrelated to PTSD symptoms. These findings suggest a complex relationship between different aspects of perceived stress and hippocampal-dependent behavior. Future analyses will test whether hypothesized reductions in perceived stress following mindfulness training are accompanied by behavioral changes indicative of improved hippocampal function.

Disclosures: **D.W. Grupe:** None. **R.J. Davidson:** Other; Founder, President and board member, Healthy Minds Innovations.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.03/ZZ11

Topic: F.03. Neuroendocrine Processes

Support: CNPq, 150959/2014-1
CNPq, 447835/2014-9

Title: What the eyes can't see the heart does not grieve over: A study of the relationship between psychological distance and the opinion on decreasing the age of criminal responsibility in Brazil

Authors: *C. P. BAHIA¹, I. F. R. CALDAS², K. FIGUEIREDO³, H. MELO², I. PAIM², P. BATAGLIA², R. MARTINS⁴, A. P. JÚNIOR²

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Abstract: The sharp increase in urban violence in Brazil. One of the proposals is to reduce the age of criminal responsibility. However, the debate on this subject has been played mostly on the political stage, without much information by science. Besides political proselytism, popular opinion is also subject to biases related to the way psychological distance weights individual information about targets of justice judgments. In the present work we compare the Kohlberg's stages of moral development and obtained from the responses of two distinct samples to a dilemma involving an adolescent breaking the law. One sample (N=77) was composed of workers from a juvenile justice court and the other (N=157) was composed of people randomly approached in a public square, both in the city of Belém, Pará State, BRAZIL. We also asked whether subjects from both samples were for or against the proposal to reduce the age of criminal responsibility currently being debated in the Brazilian parliament. Results show that juvenile court workers are mostly associated with lower Kohlberg moral stages (stage 1) and also have a lower level of moral competence (average c-index=3.97). People approached in the public

displayed a preference for higher moral stages (stage 6) and have an average c-index of 14.29. The association between stage preference and opinion on decreasing the age of criminal responsibility was significant only for the juvenile court workers ($\chi^2 = 20,665$, $df = 10$, $p = 0.024$), which were strongly against it ($p < 0.01$). These apparently discrepant results can be reconciled when one considers that court workers are psychologically closer to the juveniles during court proceedings and are thus more acquainted with their idiosyncratic characteristics, thereby being more sensitive to the targets' identity and thus assuming a less punitive stance in the application of justice.

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Poster

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Program #/Poster #: 077.04/ZZ12

Topic: G.03. Emotion

Support: Kennesaw State University Psychology Department
Kennesaw State University Office of Research
Kennesaw State University Center for Excellence in Teaching and Learning
Kennesaw State University WellStar School of Nursing

Title: The roles of estradiol and progesterone in mediating fear-potentiated startle during the acquisition and extinction of differential fear conditioning: Comparing naturally cycling women, women using hormonal contraceptives, and men

Authors: *E. M. GLOVER¹, O. LAUZON¹, J. EDMOND¹, B. SARRECCHIA¹, R. ALFRED¹, O. TYLER¹, S. PEARCEY¹, V. WAGNER²

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Abstract: Women are disproportionately diagnosed with anxiety disorders at more than twice the rates than men. There is a growing need for research examining biological underpinning of these sex disparities. Previous research has characterized estrogen as well as progesterone as playing important neuromodulatory roles in emotion regulation. However, there are mixed findings and limited understanding of the activational effects of naturally cycling hormones versus exogenous hormone exposure (via hormonal contraceptives) on emotion regulation in women contrasted with men. The current study uses the fear-potentiated startle paradigm to quantify psychophysiological correlates of emotion regulation (i.e., ability to inhibit acoustic startle responses in a safe context relative to a threatening context) in naturally cycling women, women using hormonal contraceptives, and men. Female participants were grouped as naturally

cycling (n=36) or combined oral contraceptive (COCs) users (n=36). Naturally cycling women were further divided into menstrual cycle phases (luteal, n=11 vs. follicular, n=12) according to what day they fell on the menstrual cycle at the time of testing. In addition, saliva samples were collected for analysis of circulating levels of salivary 17 β -estradiol and progesterone immediately prior to testing. All women were grouped into high vs. low estradiol or progesterone groups based on a median split of overall salivary hormone levels. There were no significant differences in fear acquisition between men and women in the luteal vs. follicular phases of their cycle. However, women with low estradiol and low progesterone showed deficits in fear extinction learning (i.e., heightened startle during extinction training) compared to women in the high estradiol and progesterone groups, and men. However, these deficits were more pronounced and significant in women using COCs [$F(2,18) = 3.73, p = .04$]. These data support previous findings that having low estrogen and progesterone may be a risk factor for the development of anxiety. They also underscore the need for assessing contraceptive use as a critical variable when attempting to understand sex differences in emotion regulation and its clinical implications.

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Poster

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Program #/Poster #: 077.05/ZZ13

Topic: G.03. Emotion

Support: NIH RO1MH098348

Title: Functional connectivity influences stress-induced changes in autonomic arousal

Authors: *H. E. DARK¹, N. G. HARNETT², A. M. GOODMAN², S. MRUG², M. A. SCHUSTER³, M. N. ELLIOT⁴, S. TORTOLERO⁵, D. C. KNIGHT⁶

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Abstract: The physiological response to stress is mediated by the functional connectivity of frontal and limbic brain regions. Specifically, the ventromedial and ventrolateral prefrontal cortex (vmPFC, vlPFC), amygdala, and hippocampus are associated with changes in skin conductance to both internal and external stimuli. Chronic stress can disrupt brain connectivity, which subsequently alters physiological arousal in response to stress. Resting state functional connectivity (rsFC) is a metric of brain connectivity patterns. Few studies have examined how

stress-induced changes in rsFC are associated with skin conductance level (SCL), and whether this relationship varies with prior life stress. The present study examined how stress-induced changes in rsFC affect the relationship between cumulative violence exposure (CVE) and stress-induced changes in SCL. Participants completed two 6-minute resting state functional magnetic resonance imaging (rs-fMRI) scans prior to (pre-stress) and after (post-stress) completing the Montreal Imaging Stress Task. SCL was assessed during each rs-fMRI scan. The amygdala and hippocampus were used as regions of interest for seed-based rsFC analyses. A linear mixed effects analysis was conducted to determine whether SCL differed pre- to post-stress as a function of stress-induced changes in amygdala- and hippocampus rsFC and CVE. A family-wise error correction ($p=.05$) was applied to all significant clusters. There were no main or interaction effects for CVE for amygdala- or hippocampus-whole brain rsFC. There was a main effect for SCL such that hippocampus-vIPFC, -dIPFC, and -inferior parietal lobule (IPL) rsFC varied with SCL. As hippocampal rsFC increased, SCL decreased. There was a significant interaction between Condition (pre- to post-stress) and SCL among hippocampus-PCC (posterior cingulate cortex), -insula, and amygdala-PCC rsFC. There was a positive relationship between hippocampus-PCC rsFC and SCL pre-stress, but not post-stress ($p<.0001$). There was a negative relationship between hippocampus-insula rsFC pre-stress, but not post-stress ($p<.002$). There was a positive relationship between amygdala-PCC rsFC pre-stress, but not post-stress ($p<.01$). Results suggest that SCL varies with the rsFC of neural circuits that support emotion expression and regulation. Greater fronto-limbic, parieto-limbic, and intra-limbic rsFC was associated with decreased autonomic arousal. SCL was associated with hippocampal-IPL, -PCC, and amygdala-PCC rsFC pre-stress, but not post-stress. Findings suggest that stress disrupts communication among neural circuits that support emotion expression and regulation.

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Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.06/ZZ14

Topic: G.03. Emotion

Support: NIH MH092576
MH098212

Title: Computational mechanisms of defensive startle in humans

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Abstract: The startle reflex is a defensive response to sensory stimuli indicating acute predatory threat. Its expression and facilitation by threat-conditioned cues is widely observed across the animal kingdom. The current understanding of underlying neural or psychological mechanisms is incomplete as it does not afford a precise quantitative prediction of startle magnitude over repeated exposures to startle probes. Here, we present a cognitive-computational model of startle habituation, and of startle potentiation during fear conditioning. In a large data set of n = 243 human participants, we demonstrate that startle habituation approximates statistically optimal learning about the lack of predatory threat in a given environment. Startle potentiation during fear conditioning combines this knowledge with the threat-predicting properties of the conditioned stimuli. Next, we analyzed data from n = 150 patients with posttraumatic stress disorder, in which globally increased startle magnitude is a frequent observation. Using model comparison, we additionally found that they use a distinct model of the environment to learn about the absence of threat. To summarize, our results provide a quantitatively precise prediction of startle magnitude over repeated trials and suggest a biologically plausible explanation for startle habituation that uses a world model, which is altered in PTSD patients. This may inform further research into the neurobiological mechanisms of startle habituation and potentiation, and their pathological alterations in clinical states.

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Poster

077. Emotion: Fear, Anxiety, and Pain I

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Topic: G.03. Emotion

Support: R01 MH099073

Title: Pavlovian fear conditioning in a naturalistic environment

Authors: ***P. R. ZAMBETTI**¹, J. J. KIM^{1,2}

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Abstract: Contemporary models of fear and their putative translational significance largely stem from rodent Pavlovian fear conditioning research, which simplifies behavioral, systems, circuit and genetic analyses of the acquisition, expression, generalization, extinction and return of a specific fear CR (e.g., freezing). However, although fear conditioning is widely held to be crucial for survival, its functions surprisingly have yet to be ethologically validated. Some have also questioned its evolutionary relevance—if associative trial-and-error learning were the primary defensive mechanism, most animals would be killed before they learned which predators and situations must be avoided (e.g., Bolles, 1970). To address this critical gap in proof of concept,

we incorporated a one-trial delay auditory fear conditioning procedure into an ethologically-relevant ‘approach food-avoid predator’ scenario. Moreover, to better simulate the predator-inflicted pain found in nature, the US was a subcutaneous dorsal body shock to mimic the predator’s strike to the prey’s head/back regions. Specifically, a tone CS (3 kHz, 85 dB) tuned-on when male and female rats entered the foraging arena. As the animals approached the food, an owl model emerged from behind a black curtain in conjunction with a delivery of the US to simulate predatory-inflicted pain. Subsequent testing showed that when the tone CS was presented in the foraging arena, all rats instantly fled to a nest and failed to retrieve the food pellet. Additionally, female rats exhibited significantly stronger and enduring fear to the CS than male rats. However, there was no generalized fear when the CS was presented in a conditioning chamber. Implementing fear conditioning during realistic prey-predator interactions provides a new avenue in understanding how the brain encodes and associates fearful situations because it simulates (unlike standard fear conditioning) real human physical/psychological trauma associated with assault, rape, and combat where there are discernible assailants.

Disclosures: **P.R. Zambetti:** None. **J.J. Kim:** None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.08/ZZ16

Topic: G.03. Emotion

Support: R01 MH099073

Title: The effectiveness of looming stimuli to elicit defensive behavior in rats engaged in a risky foraging scenario

Authors: ***B. P. SCHUESSLER**¹, P. R. ZAMBETTI¹, J. J. KIM^{1,2}

¹Psychology, Univ. of Washington, Seattle, WA; ²Neurosci., Univ. of Washington, Seattle, WA

Abstract: Neurobiological models of fear in rodents have been derived primarily from studies using Pavlovian fear conditioning, which focuses on how a particular cue, upon pairing with an aversive (usually painful) event, becomes capable of eliciting learned fear responses. Though the paradigm affords a highly controlled environment and measures a well-defined, simple behavior, it does not take into account the breadth of risky situations in nature that demand diversity in fear behavior. In contrast, ethologists contend that animals most likely rely on innate, unlearned fear of sudden stimuli (evolutionarily reliable signals of threat) that guide and shape adaptive behaviors (e.g., Bolles, 1970), as instinctive fear offers a competitive advantage over the potentially dangerous and time-consuming trial-and-error learning that occurs in fear

conditioning (e.g., Pellman and Kim, 2016). A popular innate fear paradigm in rodents (usually mice) uses overhead looming stimuli to evoke instinctive freezing and/or fleeing behaviors (e.g., Yilmaz & Meister, 2013; Wallace et al., 2016). These stimuli, generated atop testing chambers by electronic screens, include dark expanding discs, or dark horizontal sweeping bars to simulate the presence of an aerial predator, such as an owl (a common predator in rodents). However, in these studies, the chambers are typically small and the screens situated close to the animal, leading to limitations in predator silhouette approximation and restriction in choice behavior, even when shelter is provided. Thus, the present study conducted in male and female rats used a large foraging arena (29 cm L x 57-66 cm W x 60 cm H nest with a side sliding gate to a 202 cm L foraging area that widens to 114 cm W) and projector (WXGA resolution) mounted from the ceiling to produce several types of overhead stimuli: a localized expanding disc or rectangle, or a sweeping bar that covers the entirety of the arena. Females fled to a safe nest area in response to the sweeping bar stimulus that covered the entire arena, but not to the other localized stimuli. This response subsisted approximately 1-2 trials, each 20-30 seconds in duration. At no point did female subjects freeze. Male rats, conversely, did not respond to any stimuli. Future directions include projecting the stimuli upward at an angle to test whether rats can perceive the actual shapes as opposed to only their shadows, and whether there is a difference in defensive behavior under this condition.

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Poster

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Program #/Poster #: 077.09/ZZ17

Topic: G.03. Emotion

Support: NIH RO1 MH108342

Title: Anxiety-like behavior in adolescent mice is enhanced by selective knockdown of GAD67 in neuropeptide Y interneurons

Authors: *M. A. CORTES, K. M. CORDER, A. F. BARTLEY, S. LEAR, F. LUBIN, L. E. DOBRUNZ

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Abstract: GABAergic dysfunction has been implicated in a variety of neurological and psychiatric disorders, including anxiety disorders. Anxiety disorders are prevalent at all ages; however during adolescence, they are the most common type of psychiatric disorder. GABA modulation regulates anxiety behaviors, and many anxiolytic medications enhance GABAergic function. GAD67 is the enzyme responsible for the majority of GABA production, and

disruption of its gene is linked to anxiety disorders. Neuropeptide Y (NPY) expressing cells are a class of GABAergic interneurons abundantly found in brain regions associated with anxiety, including hippocampus, medial prefrontal cortex, and amygdala. Loss of NPY+ interneurons has been shown to enhance anxiety behaviors. Interestingly, a previous study showed that knockdown of GAD67 from NPY+ cells actually led to reduced anxiety behaviors in adult mice. However, it is unclear the role that GABA release specifically from NPY+ interneurons plays in anxiety at younger ages, particularly at adolescence. To test this, we used a transgenic mouse line with bacterial artificial chromosome-driven miRNA silencing that reduces GAD1 mRNA in NPY+ cells (NPYGAD1-TG), and measured effects in adolescent (1-2 month old) mice. Immunohistochemistry revealed a 40% decrease in GAD67 in NPY+ cells in prefrontal cortex, indicating a significant but incomplete knockdown of GAD67 at adolescence in the NPYGAD1-Tg mice. In contrast, there was no significant reduction of GAD67 in NPY+ cells in hippocampus. Nevertheless, adolescent NPYGAD1-TG mice have higher anxiety as measured by the elevated plus maze and open field tasks. Furthermore, NPYGAD1 mice had enhanced social dominance, a prefrontal cortex dependent innate behavior. In contrast, there was no change in contextual or cued fear learning, which depend on hippocampus and amygdala. Although our results do not rule out a possible contribution from other brain regions, our data support the idea that prefrontal cortex plays an important role in the anxious phenotype of adolescent NPYGAD1-TG mice. Our results show the behavioral impact of cell-specific interneuron dysfunction and suggest that GAD67 function in NPY+ cells is important for regulating innate behavior in adolescents.

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Poster

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Program #/Poster #: 077.10/ZZ18

Topic: G.03. Emotion

Support: NIH R01 MH108342

Title: Cell type specific overexpression of neuropeptide Y causes changes in receptor function

Authors: K. M. CORDER, Q. LI, M. A. CORTES, *L. E. DOBRUNZ
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Abstract: Neuropeptide Y (NPY) is an endogenous neuropeptide found abundantly in the central nervous system. NPY has been shown to be involved in a variety of neuropsychiatric disorders and neurological processes. In particular, NPY has been implicated in anxiety disorders and fear

learning behavior, and reduced levels of NPY are reported in patients with post-traumatic stress disorder (PTSD). Because NPY has been proposed as a potential therapeutic target for PTSD, it is important to understand the effects of chronically increasing NPY levels. Previous studies have shown that acute enhancement of NPY reduces anxiety, fear learning and locomotor activity. Baseline anxiety was reduced by viral overexpression of NPY, but was not altered in a transgenic rat model overexpressing NPY. However, NPY is normally expressed by a subset of GABAergic interneurons, providing spatially and temporally specific patterns of release. Administration of exogenous NPY throughout the brain, or chronic overexpression in cells that do not normally release NPY can have detrimental side effects, including memory impairment and cardiac dysfunction. As a result, it is imperative to determine the effects of NPY enhancement only in the cells that normally express it. We therefore utilized a transgenic mouse line that overexpresses NPY in NPY cells, thereby maintaining its normal spatiotemporal release. We tested for effects on anxiety related behaviors in mice during adolescence, an age where there is a high incidence of anxiety disorders in humans. Although there is no change in anxiety or fear learning behavior in the NPY-cell specific overexpression mice, we did observe a decrease in locomotor activity. We saw a reduction in the effect of exogenous NPY on synaptic transmission in acute hippocampal slices, indicating that the NPY receptors are desensitized or downregulated. The reduction in NPY receptor function could contribute to the heterogeneity of the behavioral effects, including the lack of effects on hippocampal dependent fear learning. We conclude that overexpression of NPY, even when only in cells that normally express it, can lead to selective receptor desensitization to NPY in adolescent mice, potentially affecting its ability to function as a therapeutic for certain disorders.

Disclosures: K.M. Corder: None. Q. Li: None. M.A. Cortes: None. L.E. Dobrunz: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 077.11/ZZ19

Topic: G.03. Emotion

Support: UFSCar

FAPESP (2015/153353; 2015/00006-4)

CNPQ (309201/2015-2)

Title: Social modulation of pain: The role of serotonergic neurotransmission within amygdaloid complex on hypernociception induced by living with a conspecific in neuropathic pain in mice

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Abstract: AIM: Several findings have been showing the involvement of serotonergic system, specifically 5-HT₃ receptors, and amygdaloid complex on modulation of emotional components of pain. Recently, our research group has shown that living with a conspecific in chronic pain is able to increase the nociceptive responses in animals subjected to the writhing test. The aim of this study was investigate the role of 5-HT₃ receptors systemically and intra-amygdala in this type social modulation of pain. **METHODS AND RESULTS:** Male Swiss mice (n=9-13/group), were housed in pairs for a period of 28 days. On the 14th day, one animal from each pair underwent constriction surgery of the sciatic nerve or not, divided into two groups: cagemate nerve constriction (CNC), in which one animal of each pair was subjected to sciatic nerve constriction; cagemate sham (CS), in which one animal from each pair was subjected to the same surgery but without constriction. On the 24th day, the mice that lived with the CNC or CS animal were subjected to a stereotaxic surgery. On the 28th day each mouse received a subcutaneous (s.c.) injections of vehicle or ondansetron (5-HT₃ antagonist) (0.08, 0.16, 0.2 and 0.32 mg/kg) and after 30 minutes, received an intraperitoneal (i.p.) injection of acetic acid (0.6%, 0.1 ml/10g) and was submitted to the whiting test (Experiment 1). In Experiment 2, the mice received bilateral injection of vehicle or ondansetron (0.3, 1.0 or 3.0nmol/0.1µl) intra-amygdala and after 5 minutes, received an (i.p.) injection of acetic acid and was submitted to the test to evaluate nociception. Two-way ANOVA (Factor 1: condition x Factor 2: treatment) followed by Duncan's test revealed significant effects for the systemic treatment factor ($F_{(4,101)}= 10.01$, $P < 0.01$), and interaction between treatment versus condition ($F_{(4,101)}= 5.56$, $P < 0.01$). The ondansetron (0.2 and 0.32 mg/kg, s.c.) decrease the writhes number in the CNC compared to the vehicle. In Experiment 2 the analysis revealed statistically significant effects for the treatment factor ($F_{(3,71)}= 23.51$, $P < 0.05$), and interaction between treatment versus condition ($F_{(3,71)}= 4.92$, $P < 0.05$). Duncan test confirmed that number of writhes was significantly higher in CNC animals compared with animals in the CS groups in both experiments. Intra-amygdala treatment (1.0 and 3.0nmol/0.1µl) attenuated the hypernociception induced by living with a pair in neuropathic pain. **CONCLUSIONS:** These results suggest that the hypernociception induced by cohabited in pairs in the chronic pain is modulates by serotonergic neurotransmission, specifically the amygdala play a significant role in social modulation of pain.

Disclosures: **A. Canto-de-Souza:** None. **L.R.R. Tavares:** None. **D.P. Ferrari:** None. **D. Baptista-de-Souza:** None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.12/ZZ20

Topic: G.03. Emotion

Support: FAPESP 2013/06764-2
PADC/FCF/Ar/UNESP
CNPq

Title: Susceptibility and resilience to the chronic social stress induce hyper and antinociception, respectively, in mice under inflammatory pain

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Abstract: Animals display different coping strategies when confronted to chronic stress, i.e. the response can be disproportional to the stimulus (susceptibility) or well adapted (resilience). This study aimed at assessing the influence of chronic social defeat stress (CSDS)-induced phenotypes in the nociception through the formalin test. Accordingly, socially defeated (for 10 days) or stress-naïve Swiss mice (n=7-31/group) were exposed to the social interaction test (SIT), on the 11th day, with (2.5 min) and without (2.5 min) an aggressor confined in a metal cage (target). Time spent in the interaction zone (IZ-proximal to the target) as well as in the corner zone (CZ-distal to the target) was recorded. The social interaction ratio (SI-ratio; time in the IZ with target+aggressor/with target empty) was used as a criteria to sort out defeated mice into resilient (SI-ratio \geq 1) or susceptible (SI-ratio $<$ 1). On the 12th day, mice were subjected to the formalin test to have recorded the time spent liking the formalin-injected paw. Susceptible mice spent less time in the IZ and more time in the CZ in the second half of the test (target+aggressor) compared to the first half (target empty); (2-way ANOVA/Duncan's post hoc test $p<0.05$). On the contrary, resilient animals kept exploring the IZ regardless the presence (2nd half) or not (1st half) of the aggressor, according to our criteria (2-way ANOVA/Duncan $p>0.05$). Importantly, whereas resilient animals presented antinociception in the inflammatory phase of the formalin test (25-35 min post formalin injection), susceptible mice showed a delayed hypernociception, also in the inflammatory phase of the test (35-40 min); (one-way ANOVA/ Duncan $p<0.05$). Results suggest two distinct phenomena; resilience-induced antinociception (RIA) and susceptibility-induced hypernociception (SIH), which might be linked to a well and mal-adapted behavior after CSDS exposure, respectively. Furthermore, it remains to be investigated whether these phenotypes-induced hyper/antinociception correlate with the recruitment of the facilitatory/inhibitory systems of pain, respectively. Financial support: FAPESP, CNPq, PADC FCF/Ar/UNESP.

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Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.13/ZZ21

Topic: G.03. Emotion

Support: FAPESP 2016/24568-4
CNPq 306556/2015-4
FAPESP 2017/25409-0

Title: N-methyl-D-aspartate (NMDA) receptor blockade in the right medial prefrontal cortex (mPFC) prevents the anxiogenic-like effect induced by left mPFC inhibition in mice

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Abstract: The medial prefrontal cortex (mPFC) is densely populated by glutamatergic neurons, which, in turn, play a role in the modulation of anxiety via NMDA (n-methyl-D-aspartate) receptor activation. Besides, recent findings have shown that synaptic inhibition (with CoCl₂) of the Left (L) or Right (R) mPFC provokes opposite effects on anxiety of mice exposed to the elevated plus maze (EPM). Here, we investigated whether the anxiogenic-like behavior induced by LmPFC inhibition is prevented by the NMDA blockade in the RmPFC of mice exposed to the EPM. Methods: Male Swiss mice (n=9-13/group) received intra-LmPFC injection of saline or CoCl₂ (1mM; 0.2 µL) and intra-RmPFC injection of saline or AP-7 (2-amino-7-phosphonoheptanoic acid, a NMDA antagonist; 0.05 nmol/0.2 µl, an intrinsically ineffective dose). Ten minutes later, each mouse was exposed to the EPM to record the conventional measures of anxiety (percentage of open-arm entries and percentage of open-arm time: %OE and %OT) and locomotor activity (frequency of closed-arm entries: CE). Results: Two-way ANOVA revealed significant effects of intra-LmPFC treatment [$F(1,40) = 4.83$; $p < 0.05$] and of Left x Right treatment interactions [$F(1,40) = 5.24$; $p < 0.05$] on %OE. Regarding to the %OT, two-way ANOVA showed a borderline effect of Left treatment [$F(1,40) = 3.10$; $p = 0.08$]. Duncan post hoc test revealed that the inhibition of the left mPFC reduced %OE ($P < 0.05$) and tended to reduce %OT ($p = 0.07$). However, these anxiogenic-like effects were not observed in mice simultaneously treated with the NMDA receptor antagonist into the RmPFC ($p > 0.20$). No treatment changed closed-arm exploration [$F(1,40) \leq 0.75$; $p > 0.3$]. These results are suggestive that the anxiogenic-like effect induced by synaptic inhibition of LmPFC is modulated by Glu-NMDA receptors located in the RmPFC, suggesting a hemispheric communication in the modulation of anxiety.

Disclosures: N. Santos-Costa: None. R.L. Nunes-de-Souza: None.

Poster

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Topic: G.03. Emotion

Support: CAPES

CNPq (306556/2015-4)

Fapesp 2017/25409-0

Title: Anxiogenesis induced by nitric oxide in the right medial prefrontal cortex depends on the activation of NMDA and CRF1 receptors located in the BNST of mice

Authors: *R. L. NUNES-DE-SOUZA¹, M. P. FARIA²

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Abstract: Previous studies have demonstrated that nitric oxide (NO) produces an anxiogenic effect when released in the right medial prefrontal cortex (RmPFC). In addition, corticotrophin-releasing factor type 1 receptor (CRF1) and n-methyl-d-aspartate receptor (NMDAr) located in the bed nucleus of the stria terminalis (BNST), a limbic area that receives neuronal projections from the mPFC, also play a role in the modulation of anxiety. This study investigated whether the anxiogenic effect provoked by intra-RmPFC injection of NOC-9 [6-(2-hydroxy-1-methyl-2-nitrisohydrazino)-N-methyl-1-hyxanamine], an NO donor, can be prevented by the blockade of CRF1 or NMDA receptors in the BNST. Male Swiss mice (n= 8-9/group) received intra-BNST bilateral injections of AP-7 (2-amino-7-phosphonoheptanoic acid, an NMDAr antagonist; 0 or 0.05 nmol/0.2µl) or CP 376395 [N-(1-Ethylpropyl)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-4-pyridinamine hydrochloride, CRF1 antagonist; 0 or 3.0 nmol/0.2µl] and, 10 min later, they received intra-RmPFC injection of NOC-9; 0 or 37.5 nmol/0.2µl]. After the drug injection procedure, all mice were individually exposed to the elevated plus-maze (EPM) to record the anxiety indices [% open arm entries (%OE) and % open arm time (%OT)] and locomotion [frequency of closed arm entries (CE)] for a 5-min period. Two-way ANOVA revealed significant effects for pretreatment (i.e. AP-7 or CP) versus treatment (NOC-9) interactions only for %OE (F_{2,44}=3.3; p<0.05) and %OT (F_{2,44}=3.3; p<0.05). Duncan's post hoc test confirmed that both intra-BNST treatments (AP-7 or CP) blocked the anxiogenic-like effect provoked by intra-RmPFC injection of NOC-9 (p<0.05). These results are suggestive that the anxiogenesis induced by NO release in the RmPFC depends on the activation of NMDA and/or CRF1 receptors located in the BNST of mice.

Disclosures: R.L. Nunes-de-Souza: None. M.P. Faria: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Topic: G.03. Emotion

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CNPq 306556/2015-4
CNPq 306557/2015-0

Title: The role of the left and right medial prefrontal cortex in the modulation of ethanol consumption induced by social defeat stress in mice

Authors: *L. CANTO DE SOUZA¹, R. L. NUNES-DE-SOUZA^{1,2}, C. DA SILVA PLANETA^{1,2}

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Abstract: The medial prefrontal cortex (mPFC) plays a role in the modulation of several behavioral responses, such as ethanol consumption induced by stressors. Recently, it has been proposed that functional lateralization of the mPFC in the control of emotional states is observed after chronic social defeat stress. In this context, it has been suggested that long periods of stress disrupt the tonic inhibitory control of the left mPFC (LmPFC) over the right mPFC (RmPFC), which, in turn, might lead to the resilience decrease, contributing to the development of maladaptive responses. Furthermore, our group has been demonstrating that after a single social defeat stress, the LmPFC plays an inhibitory role on the anxiogenic effects modulated by the RmPFC. Given that social defeat stress enhances ethanol consumption, here, we investigated the effects of chemical inhibition of the L or RmPFC through local injection of cobalt chloride (CoCl₂) on ethanol (10%) intake (drinking in the dark). In experiment 1, animals (n=5-9) received CoCl₂ or saline and were subjected to a single acute stress session of SD. In experiment 2, mice were previously exposed to chronic SD stress, and only animals exhibiting the susceptible phenotype (see protocol described by Golden et al., 2011) received intra-mPFC injection of CoCl₂ or saline (n=11-14) and were exposed to acute stress session of SD. In both experiments the ethanol intake was recorded (g/kg) during 10 days after intracerebral drug injection procedure. Our results did not show any significant effects of chemical inhibition of the L or RmPFC on ethanol consumption of mice in both experiments. Despite preliminary, our results are suggestive that the functional lateralization of the mPFC in the modulation of anxiety does not interfere on ethanol intake in mice subjected to SD stress.

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Poster

077. Emotion: Fear, Anxiety, and Pain I

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Topic: G.03. Emotion

Support: A Grant-in-Aid for Scientific Research (C) (15K10566) from the Ministry of Education, Culture, Sports, Science and Technology, Japan
Grant-in-Aid for JSPS Research Fellow (18J13473)

Title: The breakdown of free fatty acids-GPR40/FFAR1 signaling in the brain induce development of chronic pain after social defeat stress in mice

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Abstract: *Aims;* GPR40/FFAR1, one of the G-protein coupled receptors, is activated by free fatty acids (FAs). It is thought that GPR40/FFAR1 is important to regulate pain and emotion. FAs including docosahexaenoic acid (DHA) are abundantly existed in the brain. In our previous report, supplementation of DHA suppressed the pain behavior in mice. Furthermore, we have shown that chronic inhibition of the GPR40/FFAR1 in the brain during received social defeat (SD) stress prolonged the term of mechanical allodynia as compared with that of non-stressed mice. In the clinical study, it is reported that n-3 FAs contents decrease in the patients with depression. In addition, we find that exposure of forced swimming induces the reduction of DHA in the brain of mice. These results indicate that the activation of GPR40/FFAR1 signaling in the brain might be suppressing the development of chronic pain. In the present study, we analyzed the constitution of phospholipids and FAs in chronic pain model mice induced by the exposure of repeated SD stress. *Materials and Methods;* C57BL6J male mice and GPR40/FFAR1 knock out (GPR40^{KO}) male mice were exposed SD stress consecutive 10 days. A plantar incision was performed in the right hind paw of mice after SD stress. Mechanical hypersensitivity was evaluated by a von Frey filament test. The analysis of phosphatidylcholine (PC) performed with Imaging-TOF-MS. The amount of FAs was measured by LC-MS/MS. *Results;* Mechanical allodynia in non-stressed mice disappeared on day 4 after surgery. On the other hand, SD-

stressed mice caused mechanical allodynia during 21 days after incision. SD-stressed GPR40^{KO} mice showed profoundly continued mechanical allodynia during 56 days after incision. On day7 after surgery in SD-stressed mice, PC (16:0/16:0, 16:0/18:0, 18:1/20:4) was significantly decreased in the frontal cortex. The PC (18:0/18:0, 18:0/20:4, 18:0/18:1, 18:0/22:6, 18:1/22:6) was decreased in the mid-brain, and medulla oblongata. The exposure of SD stress induced increment of long chain FAs in the frontal cortex and hypothalamus. **Conclusion;** Our findings suggest that the breakdown of GPR40/FFAR1 associated with decrease of PC in the brain relate to the pain and emotion could be mediate development of chronic pain received after stress.

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Poster

077. Emotion: Fear, Anxiety, and Pain I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 077.17/ZZ25

Topic: G.03. Emotion

Title: Context aversion induced by social defeat in mice

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Abstract: Mice re-exposure to a context, where they have been socially defeated, seems to be an important factor to retrieve the averseness and induce behavioral effects. Nevertheless, the paucity of data regarding repeated aggressive or nonaggressive interactions on the repertory of behaviors induced by the context where mice interacted led us to design the present study. Here, we aimed at investigating the behavioral profile of stressed (socially defeated) or control (nonaggressive encounters) mice (re)-exposed to the apparatus where they have previously interacted with a conspecific. Also, to discriminate if the observed behavioral profile would be induced by the context or by interaction itself, we also performed the social interaction on an unfamiliar apparatus. Male Swiss mice (n=96) were individually subjected to 3 daily sessions of a 10-min habituation to an apparatus [a burrow connected to a surface through a tunnel. The surface is further divided into surface A (connected to the tunnel) and B through a wire mesh]. From the 4th to 7th day, mice interacted with an aggressive (Stressed) or nonaggressive (Control) conspecifics in the habituated apparatus (Familiar) or in an unfamiliar environment (surface

A'/B' - same dimensions, black walls and red light) comprising 4 groups; Control/Familiar (CF); Control/Unfamiliar (CU); Stressed/Familiar (SF); Stressed/Unfamiliar (SU). Interactions consisted of a 3-min social defeat stress or non-aggressive interaction in the surface, flanked with two 5-min sensory interactions (intruder confined in surface A or A'/ aggressor or non-aggressor residents confined in surface B or B'). On the 8th day, each mouse was re-exposed for 10 min to the familiar apparatus covered with either the aggressor's or its own home cage's wood shavings (environmental clue). Results showed that, when compared to the 3rd habituation, the SF group decreased the time spent in the surface A and rearing behavior, as well as the time digging the wood shaving (3-way ANOVA/Duncan's test; $p < 0.05$). SF group also increased the frequency and time of grooming in the burrow (2-way ANOVA/Duncan's test; $p < 0.05$) and the frequency of total SAP (stretched-attend postures; Kruskal-Wallis/Dunn's test; $p < 0.05$). Neither nonaggressive encounters nor unfamiliar pairing induced context avoidance as pointed out by the lack of effect in the other groups (3-way ANOVA/Duncan's test; $p > 0.05$). Our results showed that 4 social defeat episodes provoked conditioned aversion to the context in defeated mice.

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Poster

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Program #/Poster #: 077.18/ZZ26

Topic: G.03. Emotion

Support: NIH Grant AG011385
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Title: Heightened emotional contagion of fear learning in the hAPP-J20 mouse model of Alzheimer's disease

Authors: *T. M. GILL¹, P. E. SANCHEZ², J. SIMMS¹, T. GUO¹, K. HO¹, V. STURM³, J. YOKOYAMA³, B. MILLER⁴, L. MUCKE¹

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Abstract: Emotional contagion is a highly conserved form of empathy that likely promotes affective simulation and altruistic behavior among many different species. Patients with Alzheimer's disease (AD) have heightened levels of emotional contagion based on their responses to the Interpersonal Reactivity Index Personal Distress subscale, and detection of this abnormally heightened emotional response correlates with neurodegenerative tissue loss in the temporal lobe region relative to age-matched, healthy control subjects. The present study

assessed emotional contagion of fear learning in the hAPP-J20 mouse model, which simulates multiple pathological, biochemical, electrophysiological and behavioral features of AD in humans. Adult female non-transgenic (NTG) C57Bl/6J demonstrator mice underwent contextual fear conditioning, receiving three 2-second inescapable foot shocks, each of which was followed by a 2-minute observational interval. NTG and hAPP-J20 observer mice (n=14/group) viewed the fear conditioning of demonstrators through a clear acrylic divider that allowed the transmission of social, olfactory and auditory cues exhibited by the demonstrator mice during conditioning. The observers did not receive any foot shocks themselves. Demonstrator and observer mice exhibited robust increases in immobility behavior during the fear conditioning session. Both NTG and hAPP-J20 observers exhibited elevated levels of immobility behavior during the fear conditioning of demonstrator mice relative to baseline. Compared to NTG observers, hAPP-J20 observers displayed a marked increase in immobility behavior following foot shock delivery to demonstrator mice. In contrast, hAPP-J20 observers did not differ from NTG observers in their behavioral response to loud, startle tones and to the movement of an inanimate, motorized mouse decoy. These results suggest that pathological accumulation of amyloid-beta or other APP metabolites in brain enhances emotional contagion and may contribute to the abnormally heightened socio-emotional response also in patients with AD.

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Poster

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Program #/Poster #: 077.19/AAA1

Topic: G.03. Emotion

Support: NIH Grant EY022157
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Title: Parsing the neural circuits for visually-evoked emotional contagion

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Abstract: How is the emotional relevance assigned to visual perceptions? The ability to perceive the internal state of others and in turn express appropriate responses, enables organisms to adapt to their environment, and thus, is an essential trait of social animals. This process, termed emotional contagion, relies on complex neural machinery whose dysfunction is implicated in

developmental cognitive disorders, such as autism spectrum disorder. Despite considerable study of the neural correlates of emotional contagion in humans and non-human primates, we know very little about the underlying cell types, circuit architectures, and computations that drive this crucial phenomenon.

To address this issue, we developed a new behavioral paradigm that allows precise measurement of the robust behavioral responses triggered in mice (“observer”) while viewing innate defensive behaviors of conspecifics (“demonstrator”) exposed to visual threat ‘looming stimuli’. Using this “visually-evoked emotional contagion (VEEC)” assay, we asked:

- 1) Do mice visually determine and adopt the internal state of their conspecifics?
- 2) What behavioral repertoires do the observer mice perform?
- 3) Which regions in the brain drive visually-evoked emotional contagion?

We found that the freezing is the major responsive behavior of the observer mice in our VEEC assay. Autonomic responses of the observer mice revealed that this freezing behavior is caused by changes in internal state, not by the pure mimicry of the demonstrators’ behavior. Moreover, we identified a novel subset of subcortical and cortical nuclei that processes emotional contagion by screening for neurons showing differential activity under our VEEC assay. Anatomical mapping showed that one of these identified subcortical nuclei has reciprocal connections with the anterior cingulate cortex (ACC) which has been implicated in empathic responses of pain or fear both in humans and rodents. Using optogenetic and chemogenetic approaches we dissected the functional roles of the identified subcortical-ACC pathways in emotional contagion. Our results suggest that emotional contagion generated by vicarious visual threat exists in rodents and these may have common neural substrates in humans.

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Poster

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Support: IBS Grant IBS-R001-D1

Title: Nrxn3-dependent somatostatin-expressing neurons in the ACC control the degree of socially transmitted fear

Authors: *A. KIM, S. KEUM, J. SHIN, J.-H. KIM, J. PARK, H.-S. SHIN
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Abstract: Empathy is the ability to recognize and share emotions with others. The anterior cingulate cortex (ACC) is critically involved in human empathy and the acquisition of

observational fear in mice. However, molecular and cellular mechanisms in the ACC that control observational fear remain to be determined. Here, through behavior-driven forward genetic analyses in inbred strains of mice, we identified that a missense mutation in Neurexin 3 (*Nrxn3*) increased observational fear. Furthermore, mice in which *Nrxn3* was selectively deleted in somatostatin-expressing (SST⁺) interneurons showed markedly increased vicarious fear. In acute slices of the ACC of those mice, inhibitory synaptic transmission from SST⁺ neurons onto layer 2/3 excitatory neurons was impaired without affecting intrinsic excitability. Concordantly, optogenetic suppression of SST⁺ interneurons in the ACC evoked an elevation of vicarious freezing, mimicking the *Nrxn3* ablation in SST⁺ neurons, whereas activation of SST⁺ neurons obliterated acquisition of observational fear. This study indicates that *Nrxn3* is an essential molecular machinery for inhibitory synaptic transmission in SST⁺ neurons and uncovers a novel role of SST⁺ neurons-mediated inhibitory circuit in the ACC in gating the top-down computation for the expression of socially incited fear.

Disclosures: A. Kim: None. S. Keum: None. J. Shin: None. J. Kim: None. J. Park: None. H. Shin: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 077.21/AAA3

Topic: G.03. Emotion

Support: FCT PD/BD/106005/2014

Title: Oxytocin regulation of social buffering and social contagion of fear in zebrafish

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Abstract: Social animals can use information provided by the behaviour of conspecifics for adaptive decision-making (e.g. predator detection). However, the mechanisms involved in the processing of social information remain poorly understood. Moreover, although the neuropeptide oxytocin has been implicated in the regulation of social behaviour, its exact role in the modulation of social information processing remains unclear. Here, we used the response to alarm substance and the sight of alarmed conspecifics to study social transmission of information in adult zebrafish. We found that independent of sex, zebrafish exhibit less fear response in the presence of conspecifics (i.e. social buffering). Furthermore, we show that zebrafish respond to fear when conspecifics display fear response (i.e. social contagion of fear). Using zebrafish with

constitutive deletion in the oxytocin receptor gene (OXTR^{-/-}), we tested the involvement of oxytocin in social information use. We show that OXTR^{-/-} zebrafish have an impairment of both social buffering and social contagion of fear. Overall, our results provide evidence for the use of social information in threat perception in zebrafish, and suggest an involvement of oxytocin in this phenomenon.

Disclosures: I.D. Akinrinade: None. G. Levkowitz: None. R.F. Oliveira: None.

Poster

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Program #/Poster #: 077.22/AAA4

Topic: G.03. Emotion

Support: UFSCar
CNPQ
FAPESP (Proc.2015/00006-4)

Title: Empathy for pain: Heterogeneity activation of anterior cingulate cortex, insula and amygdaloid complex in mice living with a conspecific in chronic pain

Authors: *D. B. SOUZA¹, R. L. NUNES-DE-SOUZA², A. CANTO-DE-SOUZA³
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Abstract: The ability to capture emotional signals in the other is directly related to the survival of the species, and this feature is given the name of empathy. It has been shown that pain-related behaviors are bidirectionally influenced by other animal behavior, so to see a conspecific with pain can increase or decrease the sensation of pain in the observer mouse. Recently, our research group has shown that living with a conspecific in chronic pain is able to increase the nociceptive responses in animals subjected to the writhing test. In addition, chemical inhibition of amygdala and insula, respectively, enhances and attenuates the hyperalgesia. **Aim:** Here we investigated the activation pattern of the anterior cingulate, insular cortices and amygdaloid complex (e.g., central, lateral and basal nuclei) in mice living with a conspecific in chronic pain. Brain activation was recorded through FosB expression in each area of both hemispheres. **Methods:** Male Swiss mice (n=6-7/group) were housed in pairs for 28 consecutive days. On day 14th, pairs of mice were grouped as follow: cagemate nerve constriction [CNC; i.e. one animal from each pair was subjected to sciatic nerve constriction (SNC) surgery] or cagemate sham (CS; i.e. one animal from each pair was subjected to SNC sham surgery). After that, each pair was returned to its homecage to live together for further 14 days. On testing day (day 28th), the observer cagemates were sacrificed and their brains removed for immunohistochemistry assay. **Results:**

Student *t* test revealed that the CNC group displayed higher number of abdominal writhes ($t_{(14)}=5.83$; $P < 0.05$). Two-way ANOVA [Factor 1: condition (SNC or SG), Factor 2: hemisphere (left or right)] revealed decreasing of the activation in the anterior cingulate cortex ($F(1,20)=18.52$; $P < 0.05$) of the SNC group compared to the sham group. In contrast, SNC group showed an increase of FosB bilaterally in the insular cortex ($F(1,20)=28.46$; $P < 0.05$). ANOVA also revealed a decrease of activation of the central nucleus in the left amygdala ($F(1,20)=5.36$; $P < 0.05$) and no differences in the activation of the amygdala basal ($F(1,20)=0.56$; $P > 0.05$) and lateral ($F(1,20)=0.72$; $P > 0.05$) nuclei in SNC animals.

Conclusion: These results demonstrate that living with a mouse subjected to SNC induces hyperalgesia and alters the activation pattern of the anterior cingulate, insular cortices and amygdaloid complex. Taken together, the present results suggest the involvement of brain areas that are known to play a role in emotional states, such as anterior cingulate cortex, insula and amygdaloid complex in the modulation of pain empathy in mice.

Disclosures: D.B. Souza: None. R.L. Nunes-de-Souza: None. A. Canto-de-Souza: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.23/AAA5

Topic: G.03. Emotion

Support: Grant-in-Aid for Scientific Research(B) 16H02839

Title: Enhancement of empathy for other's pain by vicarious reward: A skin conductance response study

Authors: *M. NAKAJIMA¹, S. SHIMADA²

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Abstract: Vicarious reward is a reward received by watching likable others obtaining a positive outcome. Several studies have suggested the correlation between vicarious reward and the sense of unity with the others. However, it has not been examined how vicarious reward enhances the sense of unity. In this study, we investigated whether the degree of empathy for other's pain, which was measured as the skin conductance response (SCR), was modulated by vicarious reward received beforehand. Nineteen healthy right-handed participants (mean age 22.6 ± 0.8 ; 2 females) took part in this study. The experiment consisted of two tasks: the empathy task and the stopwatch (SW) task. The empathy task was conducted before (pre-SW) and after (post-SW) the SW task. In the empathy task, the participant watched a 4-s pain movie stimulus. In the movie, the right-hand of an agent wearing a blue or yellow glove was stabbed with a needle of a syringe, which would cause the empathy for other's pain in the participant. Participants watched the

movie stimulus of both agents two times each. In the SW task, participants watched a 7-s movie stimulus in which the right hand of the agent (wearing a blue or yellow glove) performed the stopwatch (SW) game, in which the agent has to press a button of the stopwatch to fall within ± 0.05 s of the 5.00 s time point. The SW task aims to give participants vicarious reward by observing the other's success. In this experiment, the participant selected an agent (blue or yellow) before the SW task. The participant was instructed that the honorariums increase every time the selected agent succeeded in the SW game and decrease every time the other agent succeeded. The success probability of SW game was adjusted to 80% for the selected agent and 20 % for unselected agent. Two-tailed t-test was used to see whether the vicarious reward modulates SCR. The result showed that SCR for the other's pain in the post-SW empathy task was significantly greater for the selected agent than for the other agent ($t(18) = 2.10, p < 0.05$). Our results showed that receiving vicarious reward enhances empathy for pain towards that agent.

Disclosures: M. Nakajima: None. S. Shimada: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

Location: SDCC Halls B-H

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Program #/Poster #: 077.24/AAA6

Topic: G.03. Emotion

Title: Is empathy for pain unique? A meta-analysis of neuroimaging studies of empathy

Authors: *I. TIMMERS, C. A. KRONMAN, A. L. PARK, M. D. FISCHER, L. C. HEATHCOTE, J. M. HERNANDEZ, L. E. SIMONS
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Abstract: Empathy is an essential part of being a social animal. It allows understanding and sharing of emotions and promotes prosocial behavior. When we observe someone in pain, our behavior is also largely motivated by empathy. Evidence suggests that a core neural network, including anterior insula (AI) and mid-cingulate cortex (MCC), is associated with empathy for pain. However, a similar network has been revealed for other non-pain affective states, raising the question whether empathy for pain is unique in its neural correlates. We performed an activation likelihood estimation (ALE) meta-analysis of neuroimaging studies of empathy to identify neural correlates of empathy, and commonalities and differences between empathy for pain and for non-pain affective states.

We screened 2051 titles/abstracts and reviewed 433 papers. We included papers with healthy participants, an empathy paradigm during functional imaging (fMRI/PET), and coordinates contrasting an empathy condition with baseline/neutral condition. 129 papers were included, reporting 165 relevant contrasts. GingerALE 2.3.6 was used to calculate the ALE for each voxel

and to threshold output images.

Synthesizing neural correlates of empathy confirms a core network, including AI and MCC, as well as inferior frontal gyrus (IFG), primary somatosensory cortex (SI), amygdala and periaqueductal grey (PAG) (Figure 1A). Figure 1B shows neural correlates of empathy for pain overlaid on empathy for non-pain affective states. A conjunction analysis confirms shared correlates including left AI, IFG and amygdala. Empathy for pain, however, shows unique involvement of several brain regions, including the right AI, MCC, and SI.

Taken together, our findings show that empathy for pain and empathy for non-pain affective states share neural correlates, but that empathy for pain also has unique features. This data highlights the specificity of neural circuitry of empathy for pain. Next steps include additional contrasts within empathy for pain, investigating the effect of using different experimental paradigms to elicit empathy for pain.

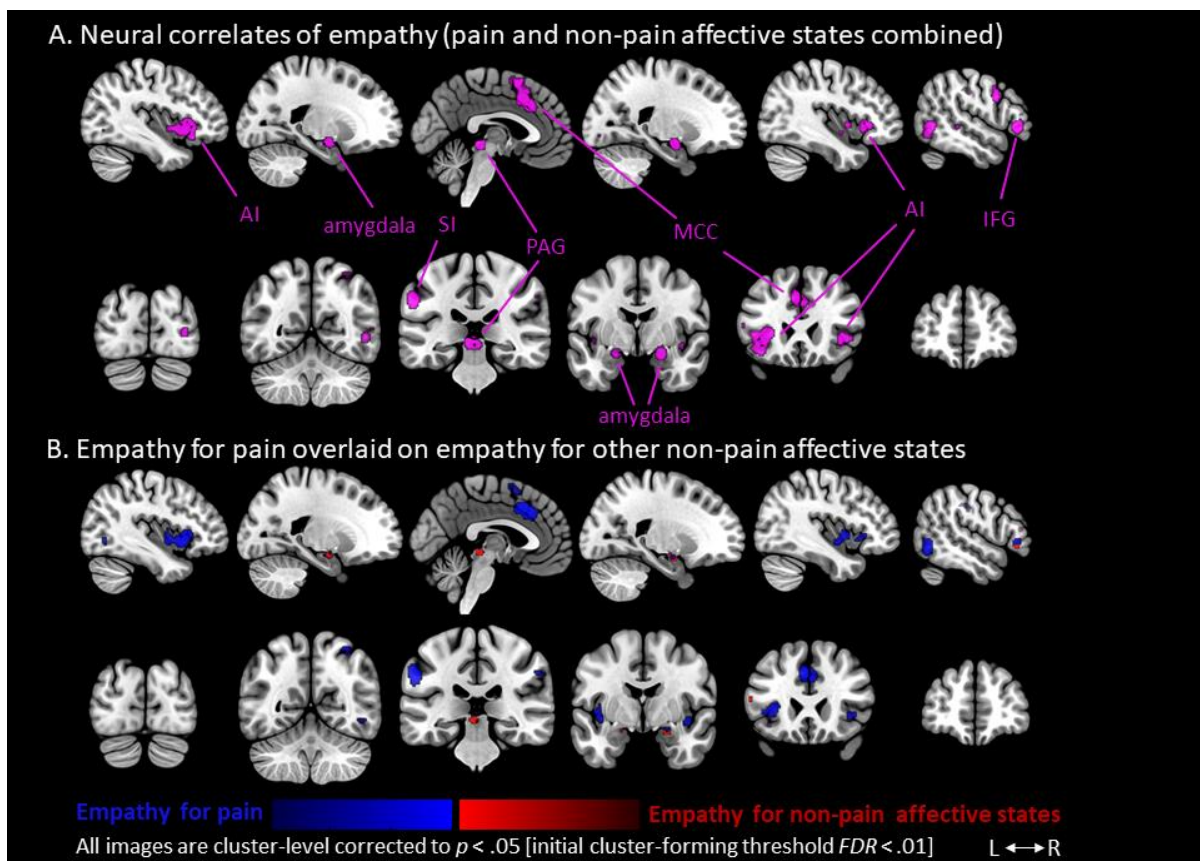


Figure 1. Overview of results from the ALE meta-analysis of empathy studies

Disclosures: I. Timmers: None. C.A. Kronman: None. A.L. Park: None. M.D. Fischer: None. L.C. Heathcote: None. J.M. Hernandez: None. L.E. Simons: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.25/AAA7

Topic: G.03. Emotion

Support: PROGRES Q35
260388/SVV/2018

Title: The role of empathy in own pain perception and pain estimation by others

Authors: *A. YAMAMOTOVA, P. DURATNA, Z. FELLEROVA, A. MOROZOVA, K. GEIER

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Abstract: Empathy is complex phenomenon characterized by understanding and ability to share feelings of another person. Observing pain of others induces emotions which are activated by mental representation of pain in self. Intensity of such “pain” should be dependent on previous experience with similar situation. Aim of our study was to test the ability to estimate pain intensity of others in dependency on empathy assessed by Toronto Empathy Questionnaire (TEQ) and on the previous experience with the same painful procedure.

Sixty healthy university students (30 men, 30 women, age 23-27 years) were tested in dyadic interaction during conditioned pain modulation (CPM). The withdrawal latencies to radiant heat stimulus delivered to three fingers of the right hand were measured twice, before and immediately after the end of tourniquet applied to the left arm (pressure 220 mm/Hg for 2 minutes). Prior to the measurement, TEQ was administered to both subjects. After the CPM tested person evaluated on the visual analogue scale own pain intensity and unpleasantness induced by tourniquet and in parallel the second person (observer) assessed the pain of the tested person. Then their roles were changed. Associations between empathy score and self-reported vs observed pain intensity were analyzed from the point of view of both persons in dependency on the order of testing.

In unfamiliar situation, more empathic persons perceived more pain ($r = 0.38$; $p = 0.04$), they looked more pain sensitive to observers ($r = 0.51$; $p = 0.004$) and their pain was overestimated (difference between observed and self-reported pain) ($r = 0.56$; $p = 0.001$). In familiar situation there was no association between empathy and neither own nor observed pain by others ($r = -0.04$; $p = 0.83$, $r = 0.92$; $p = 0.63$, respectively). More empathic persons estimated pain of others as more painful independently on the order of testing (First: $r = 0.41$; $p = 0.03$, Second: $r = 0.48$; $p = 0.007$), however, in unfamiliar situation they overestimated pain of others while after own experience they had a tendency to underestimate pain of others ($r = 0.38$; $p = 0.04$, $r = -0.29$; $p = 0.10$, respectively).

Empathy does not help to better estimate the pain of others. In familiar situation empathy decreases own pain. More empathic people look more pain sensitive to others and their pain is overestimated by them. We have a tendency to underestimate pain of less empathic persons which might be an important warning for clinicians to avoid underestimation of pain in less empathic patients.

Spreng RN et al. The Toronto Empathy Questionnaire: scale development and initial validation of a factor-analytic solution to multiple empathy measures. *J Pers Assess* 2009, 91:62-71.

Disclosures: **A. Yamamotova:** None. **P. Duratna:** None. **Z. Fellerova:** None. **A. Morozova:** None. **K. Geier:** None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

Location: SDCC Halls B-H

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Program #/Poster #: 077.26/AAA8

Topic: G.03. Emotion

Support: SFN

Title: The influence of context on the recognition of facial expressions of pain

Authors: ***G. DIRUPO**, V. DI PAOLO, E. G. LETTRY, C. CORRADI-DELL'ACQUA
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Abstract: The ability to correctly diagnose pain from others' faces is critical for healthcare systems, especially for those individuals intellectually/linguistically unable to provide a verbal report. However, pain expression is difficult to disentangle from other states (especially disgust), thus opening the issue of whether complementary sources of information might help the diagnostic process. Here, we tested the hypothesis that the context in which the facial expression is perceived can influence its recognition and evaluation. In this framework, we implemented a task to examine the influence of short contextual information on the evaluation of spontaneous expressions of pain and disgust. We asked to a sample of 39 participants to evaluate videos of pain and disgust expressions, after the presentation of a contextual sentence suggestive of a congruent or incongruent, state. Across two separate tasks, participants had to either classify the state of the observed face, or rate its associated unpleasantness. Results from the classification task revealed that incongruent contexts lead to increased amount of errors, as faces are more likely to be categorized consistently with the state suggested by the context. Furthermore, contextual information influence the rating task, as faces are evaluated as more unpleasant if preceded by an incongruent context. Overall, these data reveal that contextual information can influence the appraisal of face contractions, even in tasks where the state of the observed person is not explicitly investigated. Analysis of the neural responses associated to these tasks enlighten

the networks processing the information of the face and the one of the context involved in the recognition of a specific state and those regions where the two are integrated.

Disclosures: G. Dirupo: None. V. Di Paolo: None. E.G. Lettry: None. C. Corradi-Dell'Acqua: None.

Poster

077. Emotion: Fear, Anxiety, and Pain I

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Program #/Poster #: 077.27/AAA9

Topic: G.03. Emotion

Support: Psi Chi Undergraduate Research Grant

Title: Pain perception in non-suicidal self-injury

Authors: H. RHODES¹, K. SHEFFIELD¹, C. DE GUZMAN¹, S. DUNNA¹, *J. A. BOYETTE-DAVIS²

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Abstract: Previous research shows that people who engage in non-suicidal self-injury (NSSI) have key differences in their baseline biopsychological state compared to the general population, and these differences may help motivate NSSI behavior. Specifically, they have altered opioid signaling and increased symptoms of psychological dissociation. It was hypothesized that the pain-inducing experience of NSSI releases β -endorphin, which alleviates aversive dissociative symptoms and thus makes the behavior rewarding. The present study investigated this potential mediating effect of pain on β -endorphin release and dissociative symptoms, and compared these effects between those who do ($n = 9$; 2 males, 7 females) and do not ($n = 18$, 4 males, 14 females) engage in NSSI. Participants ($n = 27$) provided self-reports of dissociative symptoms and affect before and after a painful stimulus (Cold Pressor Test; CPT) as well as ratings of pain intensity at their pain threshold and tolerance during the CPT. No differences were found for baseline dissociative scores ($p = .898$), baseline affective arousal ($p = .373$), or pain intensity at threshold ($p = .603$) between the two groups. However, the time required to reach pain threshold was significantly negatively correlated with baseline affective arousal in the self-injuring group ($r = -.727$, $p = .026$) but not in the non-self-injuring group ($r = .150$, $p = .579$). Additionally, ELISA immunoassays were used to quantify pain-induced β -endorphin release. Analysis revealed differential release of β -endorphin in self-injurers and non-self-injurers according to their pain-induced changes in dissociative symptoms and affective state. This study demonstrates the importance of investigating the pain-induced biopsychological changes that underlie and motivate the harmful condition of NSSI.

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Poster

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Topic: G.03. Emotion

Support: National Natural Science Foundation of China 31421091
National Natural Science Foundation of China 31371123
National Natural Science Foundation of China 81471130

Title: ER β and GPER in rostral anterior cingulate cortex contribute to pain-related aversion

Authors: *K. ZANG¹, X. XIAO¹, L. CHEN¹, Y. TANG¹, H. CAO¹, L. ZHANG², Y. ZHANG¹
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Abstract: Estrogen has been proven to participate in pain-related negative emotion in the rostral anterior cingulate cortex (rACC). It is not clear which subtypes of estrogen receptors (ERs) are involved in this function. In this study, we observed that all the three types of ERs (ER α , ER β and GPER) were abundantly distributed in the rACC, especially in excitatory pyramidal neurons. Intra-rACC administration of ER β antagonist PHTPP (0.5 ng /hemisphere) and GPER anagonist G15 (0.9 ug/hemisphere), rather than ER α antagonist MPP (0.5ng /hemisphere) significantly blocked the F-CPA, furthermore, silencing of ER β , not ER α by shRNA significantly blocked the F-CPA , too. ER β agonist DPN and GPER agonist G1, not ER α agonist PPT rapidly elicited NMDA-long-term potentiation (LTP) in rACC slice. Adminisrating of ER β agonist DPN (0.01 ng /hemisphere) and GPER agonist G1 (0.1 ug/hemisphere) into the rACC directly produced conditioned place aversion without noxious stimulation. The phosphorylation level of AKT and the catalytic subunit of PKA were quickly increased after formalin stimulation. Intra-rACC administration of PI3K/ AKT antagonist wortmannin and cAMP/ PKA antagonist Rp-cAMP both blocked the F-CPA. Incubating with estrogen rapidly increased the phosphorylation of AKT and the catalytic subunit of PKA, and the increase of the phosphorylation of AKT was blocked only by pretreatment with GPER antagonist G15, oppositely, the increase of phosphorylation level of the catalytic subunit of PKA was blocked only by pretreatment with ER β antagonist PHTPP. Together, we propose that ER β through cAMP/ PKA signaling pathway, and GPER via PI3K/ AKT signaling pathway rapidly regulate the NMDA-related synaptic plasticity to participate in the pain-related aversion, whereas ER α is not required in this process.

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Poster

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Topic: G.03. Emotion

Support: National Natural Science Foundation of China 31421091
National Natural Science Foundation of China 81471130
National Natural Science Foundation of China 31371123
National Natural Science Foundation of China 31420103903

Title: The interaction between chronic pain and depression on the onset and exacerbation in parallel rodent strains

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Abstract: This study was aimed to comprehensively investigate the interaction between chronic pain and depression on the onset and exacerbation with each other, and compare different rodent strains/species in two validated pain/depression models. The trigeminal neuralgia (TN) and learned helplessness (LH) models were established on three independent strains. The TN model was prepared by chronic constriction injury to the unilateral infraorbital nerve (CION); the LH model was induced by inescapable electric foot-shocks. The depressive/anxiety-like behaviors were assessed by the open field test, elevated plus maze, active avoidance shuttle box test and forced swimming test; the mechanical allodynia was assessed by the von Frey test. The antidepressant clomipramine and the analgesic pregabalin were i.p. injected to determine whether treatment of one disease could attenuate the other which was originated from the former. Moreover, CION+LH combined stress was applied to observe the potential exacerbating effect. For Wistar rats and C57BL/6J mice, the TN model developed depressive/anxiety-like behaviors and the LH model developed hyperalgesia behavior. Comparatively, SD rats showed a higher resilience to distress. Clomipramine counteracted the LH induced depressive/anxiety disorders and LH developed hyperalgesia; pregabalin attenuated CION induced hyperalgesia and CION developed depressive/anxiety disorders. They couldn't challenge the nociceptive or depressive behavior derived from the state they don't target. Finally, aggravated depressive-like and hyperalgesia behaviors were found under the combined stress compared with LH alone. These findings reveal that pain and depression could develop into each other, but different resilience exists among strains. Combined stress partially exacerbates pain and depression.

Disclosures: L. Chen: None. Q. Guo: None. L. Yang: None. J. Yu: None. Y. Zhang: None.

Poster

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K99DA043609

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HHMI Gilliam Fellowships for Advanced Study

HHMI Investigator

Title: An amygdalar neural ensemble encoding the unpleasantness of painful experiences

Authors: *G. F. CORDER¹, B. AHANONU², B. F. GREWE⁴, M. J. SCHNITZER⁵, G. SCHERRER³

¹Stanford Univ., Palo Alto, CA; ²Dept. of Biol., Stanford Univ., Stanford, CA; ³Anesthesia, Stanford Univ., Palo Alto, CA; ⁴Inst. of Neuroinformatics, ETH Zurich, Zuerich, Switzerland; ⁵Depts. Biol. & Applied Physics, Stanford Univ. Dept. of Biol., Stanford, CA

Abstract: An unpleasant percept dominates the affective component of pain, which provides a motivational drive to initiate protective behaviors that limit exposure to noxious stimuli. While detailed mechanisms underlying the sensory detection and spinal processing of nociception have been uncovered, it remains unclear how brain circuits transform this emotionally inert information into an affective pain perception. Injury-induced plasticity within affective circuits, such as the basolateral amygdala (BLA), may lead to a miscoding of sensory information concomitant with the emergence of chronic pain. To identify the principles of nociceptive information coding in the BLA, we used a head-mounted miniature microscope to monitor the calcium activity dynamics of individual BLA neurons in freely behaving mice presented with a diverse set of painful and innocuous stimuli. We tracked the longitudinal dynamics of BLA neural coding across thousands of cells before and after the development of peripheral nerve injury-induced neuropathic pain. We found that prior to nerve injury, multidimensional and population vector analysis of stimulus-locked calcium transients revealed that a unique nociceptive neural ensemble in the BLA, distinct from positive valence ensembles, encodes a diverse array of painful stimuli. Silencing of this ensemble alleviated pain affective-motivational behaviors without altering the detection of noxious stimuli, withdrawal reflexes, anxiety, or reward. After the establishment of neuropathic pain, the ensemble representations of prior innocuous and noxious stimuli became more similar. Collectively, our results identify a neural

representation of nociception in the amygdala that is necessary for the instantiation of the negative affective qualities of acute and chronic pain.

Disclosures: **G.F. Corder:** None. **B. Ahanonu:** None. **B.F. Grewe:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix, Inc. **G. Scherrer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epiodyne, Inc..

Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

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Program #/Poster #: 078.01/AAA13

Topic: G.03. Emotion

Support: NIH Grant 5R01DA040688-02

Title: Differential regulation of migraine-associated pain and negative affect by central and peripheral delta opioid receptors

Authors: ***I. DRIPPS**, L. MOYE, A. TIPTON, A. PRADHAN
Univ. of Illinois At Chicago, Chicago, IL

Abstract: Migraine is a common and debilitating disorder that is inadequately addressed with current treatments in many patients. The delta opioid receptor (DOR) shows promise as a novel target for migraine treatment. In rodent models, DOR agonists have been shown to inhibit migraine-associated pain and negative affect without the abuse potential and opioid-induced hyperalgesia (OIH) associated with mu opioid receptor agonists such as morphine. DOR agonists can also block OIH, an effect that encourages the development of DOR agonists for medication overuse headache. DORs are expressed in several peripheral and central regions important for pain processing and mood regulation, and it remains unclear which receptors are critical for regulating these anti-migraine effects. To this end, we examined the ability of the DOR agonist SNC80 to inhibit migraine-associated allodynia and negative affect, as well as OIH in conditional knockout mice with DORs deleted from specific central or peripheral regions. One mouse line lacks DORs in peripheral neurons (Nav1.8-DOR KO) while the other lacks DORs in GABAergic forebrain neurons (Dlx5/6-DOR KO). Migraine-associated allodynia was produced using nitroglycerin (NTG), a known human migraine trigger. OIH was produced by administering morphine twice a day for four days. These pain states were assessed via mechanical stimulation of the periorbital region with von Frey filaments. Migraine-associated negative affect was assessed using conditioned place aversion to a single dose of NTG. SNC80 fully inhibited NTG-induced periorbital allodynia in Nav1.8-DOR KO mice and wild-type

littermates. However, in Dlx5/6-DOR KO mice, SNC80 failed to inhibit allodynia produced by NTG. SNC80 inhibited OIH in wild-type mice, but did not have a significant effect in either Nav1.8-DOR or Dlx5/6-DOR KO mice. SNC80 inhibited conditioned place aversion produced by NTG in Nav1.8-DOR, but not Dlx5/6-DOR KO mice. Overall, these data suggest that central DORs are more important for the anti-migraine effects of DOR agonists, whereas both central and peripheral DORs are necessary for the anti-OIH effects. Future work will further evaluate the role of DORs within individual brain regions on migraine-associated pain, negative affect, and cortical spreading depression.

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Poster

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Title: Effects of the serotonergic agonist meta-chlorophenylpiperazine (mCPP) on OCD-like behaviors in rats

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Abstract: Mental disorders are currently the leading cause of disability worldwide. Among them, Obsessive-Compulsive Disorder (OCD) affects about 2 to 3% of the population. Considering OCD prevalence, its strong impact on the welfare of patients and their relatives, and the large number of treatment-resistant patients, more studies examining its pathophysiology could lead to the optimization of therapeutic approaches. Although mechanisms underlying OCD pathophysiology are not fully elucidated, clinical studies and animal models strongly suggest a serotonergic dysfunction in this disorder. In this direction, the 5-HT_{2c} serotonergic agonist meta-chlorophenylpiperazine (mCPP) worsens symptoms in untreated OCD patients. In the present study we evaluated the effects of mCPP on the expression of OCD-like behaviors in rats. Male Wistar rats received intraperitoneal administration of mCPP (0.0, 0.1, 0.5, 1.0 or 3.0 mg/kg) and had the self-grooming behavior scored for 20 min immediately after drug treatment. Next,

different cohorts of animals were submitted to the marble burying, nestlet shredding, spontaneous alternation, compulsive checking and open-field tests. mCPP increased self-grooming expression and decreased spontaneous alternation in a dose dependent manner. mCPP did not induce compulsive checking or compulsive-like burying or shredding behaviors. All mCPP doses used impaired the motor activity of the animals, decreasing the distance travelled and the frequency of rearings, and increasing immobility in the open-field test. In general, the present data indicate that exacerbated grooming and impaired spontaneous alternation could be similarly mediated. Also, the aforementioned mCPP effects seem to occur independently of the decrease in the exploratory activity caused by the drug. The results suggest that, although limited, the mCPP-pharmacological model is consistent with an OCD-like profile in rats and highlight the potential role of 5-HT_{2c} receptors in OCD pathophysiology. In addition, the results indicate that the use of data from multiple behavioral assays may be advantageous when addressing a multifaceted mental disorder as OCD.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

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Program #/Poster #: 078.03/AAA15

Topic: G.03. Emotion

Support: CAPES/PROEX

Title: Environmental enrichment prevents anxiety-like behavior and decrease the expression of neuronal nitric oxide synthase in the hippocampal formation in rats exposed to different types of chronic stress

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Abstract: Adaptive responses to stress may be accompanied by changes in emotional behaviors, in particular related to fear and anxiety, as well as changes in pain sensitivity. These changes have been associated to modifications in brain areas related to defensive behavior mediated by nitric oxide. Furthermore, evidences have shown that environmental enrichment improves memory processes, learning and nociceptive responses. However, the relationship between chronic stress and the advantages of using environmental enrichment, and the participation of nitric oxide in these processes are still poorly investigated. The study aimed to investigate

whether environmental enrichment promotes alteration of the emotional behavior, nociceptive sensitivity, as well as immunoreactivity to neuronal nitric oxide synthase (nNOS) in the central nucleus of the amygdala (CeA), hippocampal formation and dorsolateral periaqueductal gray matter (dIPAG) in rats submitted to social isolation stress (SI) or chronic unpredictable stress (CUS) and reared in enriched environment (EE) or standard environment (SE). Male *Wistar* rats (~ 70g) were randomly divided into two major experimental groups: SE or EE, maintained for 38 days. Each group was subdivided according to the type of chronic stress: Control (without stress - C), SI (for 38th days) and CUS (from day 28 to day 37). At day 38, the rats were evaluated for emotional behavior by elevated plus maze (EPM) and light/dark box (LDBT) tests and nociceptive sensitivity by the hot plate test (which was performed in two steps: day 0 and day 38). Euthanasia occurred on day 39, to collect the brain for nNOS immunoreactivity analysis. Taking into account emotional behavior and nociceptive sensitivity, SI and CUS decreased the percentage of time, the frequency of entry of the open arms, end-arm exploration and the head dipping frequency in the EPM, despite of not altering the nociceptive sensitivity. On the other hand, EE increased the percentage of time, the frequency of entry of the open arms and the end arm-exploration in the EPM, although it did not alter the nociceptive sensitivity. Increased immunoreactivity to nNOS in hippocampal formation was observed in SI and CUS. In particular, in the CA3 region there was a significant interaction between stress factors due to SI and rearing environment. Thus, the results suggest that nNOS in the hippocampal formation plays an important role in the anxiogenic effect exerted by the different types of chronic stressors (SI and CUS) and it is suggested that EE can prevent the anxiety-like behavior.

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Poster

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Title: Molecular approach of circadian regulation of mouse anxiety-like behavior

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Abstract: Circadian regulation of physiology extends to higher brain functions including cognition and memory, such that time-of-day-dependent variations in cognitive performance and

memory formation have been described in various species. We had found that consolidation of long-term memory formation for object recognition is circadian regulated with the peak during the early subjective night, which is blunted by disruption of the hippocampal clock in mice (Shimizu *et al.* Nat Commun 2016). Disturbances in human activity rhythms such as those arising from shift work or jet lag increase the risk for mood disorders. In rodents, perturbations of the circadian clock by means of surgical, genetic, pharmacological or light-induced manipulations lead to a spectrum of abnormalities in emotionality-related behaviors, including elevated or attenuated anxiety-like behaviors. While these lines of evidence show that disruption of the circadian clock triggers a spectrum of affective abnormalities, how the clock regulates mammalian emotionality remains unclear. We sought to unravel the mechanisms governing mammalian anxiety regulation and characterized temporal regulation of mouse anxiety-like behaviors by the circadian clock. We show that anxiety-like behaviors are expressed in a circadian manner in mice and demonstrate that the clock machinery in the dorsal telencephalon is required for the time-of-day-dependent regulation of anxiety-like behaviors. We identify SCOP/PHLPP1 β (suprachiasmatic nucleus circadian oscillatory protein) as an essential intracellular signaling molecule mediating this temporal regulation downstream of the clock. SCOP is a signaling molecule originally identified as a gene product whose expression oscillates in a circadian manner in the rat SCN (Shimizu *et al.* FEBS Lett 1999). SCOP protein is predominantly expressed in the central nervous system, and has been shown to regulate a range of intracellular signaling pathways (Shimizu *et al.* Cell, 2007). Using viral-mediated, basolateral amygdala (BLA)-specific knockout of *Scop*, we demonstrate that deletion of SCOP in the BLA exerts anxiolytic effects on the elevated plus maze at early subjective night, thereby blunting the circadian variation in the anxiety-like behavior. We conclude that the circadian expression of SCOP in the BLA plays a key role in generating circadian rhythmicity in the anxiety-like behavior. Our results demonstrate SCOP as a regulator of anxiety-like behaviors and reveal its key role in the anxiogenic functions of the BLA. (Nakano *et al.* Sci Rep, 2016)

Disclosures: K. Shimizu: None. J. Nakano: None. Y. Fukada: None.

Poster

078. Emotion: Fear, Anxiety, and Pain II

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IBS-R026-D1

Title: The mechanisms to modulate anxiety behavior in female estrous cycle

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Abstract: Mental disorders, generally characterized by some combination of abnormal thoughts, emotions, behavior and relationships with others, affect one in four people (around 450 million people) in the world. The most common mental illnesses are anxiety and depressive disorders, affecting 260 million and 300 million people, respectively. Surprisingly, the prevalence of stress- and fear-related disorders, such as major depressive disorder, anxiety disorder and post-traumatic stress disorder, is higher in women than men. Although it is supposed that these phenomena may be caused by sex differences in biological and pharmacological factors, most researches investigating neural mechanisms of mental disorders has been limited to the use of male rodent models due to variance in female hormone levels. To elucidate the neurobiological mechanisms of anxiety disorders in consideration of sex difference, we focused on female estrous cycle, recurring physiological changes that are induced by reproductive hormones, by using naive male and female mice. We observed that anxiogenic behavior of female mice was fluctuated according to female estrous cycle, and caused by the changes of tonic GABA level in hippocampus. Also, we have studied these neural mechanisms in anxiety disorder to find out the relationship between the vulnerability of mental disorder and sex differences.

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Poster

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Title: A comparison of the successive alleys test and three more common measures of anxiety-like behavior in male and female Long Evans rats

Authors: *A. BALDASSARO¹, J. WEINER²
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Abstract: Emotions like anxiety are complex, multidimensional constructs comprised of many distinct elements. Although there are many validated behavioral assays used to measure anxiety-like behavior in animals, which elements of “anxiety” these assays assess is often not clear.

Nevertheless, a common assumption is that these assays are measuring the same elements of anxiety-like behavior. In addition, many studies use these tests to examine sex differences but it is not known if these assays assess the same elements of anxiety-like behavior in males and females. Here, we begin to address these questions by characterizing the successive alleys test (SAT), a novel rodent assay of anxiety-like behavior. This assay consists of a linear series of four alleys, each with increasing anxiogenic properties, that may offer advantages over more common tests of anxiety-like behavior. The “anxiety” gradient created by the four distinct alleys may increase the sensitivity of this assay relative to more traditional tests that only offer a binary choice (e.g. open/closed arms). Male and female Long Evans rats were run on the SAT as well as three other validated assays of anxiety-like behavior, the open field, elevated plus-maze, and zero maze. Male rats spent the majority of their time in the enclosed arm of the SAT and proportionately less time on each of the successive alleys. Females spent less time than males in the enclosed alley and their time on the three successive alleys was relatively similar, suggesting that females exhibited less anxiety-like behavior than males on this assay. Sex differences in anxiety-like behaviors were also observed in the zero maze but not the plus maze or open field. In addition, time on the open arm of the SAT did not correlate with similar measures on any of the other tests. These data provide additional evidence supporting the validity of the SAT to measure anxiety-like behavior. The observation that sex differences and open arm measures did not correlate across these tests suggests that these assays are measuring distinct elements of anxiety-like behavior. Additional studies will be needed to further characterize the nature of these differences as well as the sexually dimorphic behavioral responding across the different tests.

Disclosures: A. Baldassaro: None. J. Weiner: None.

Poster

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Title: Behavioral consequences of disrupted circadian clock function within the mouse striatum

Authors: *K. SCHÖTTNER, M. BUTTON, J. GOLDSMITH, P. SOLIS, N. DE ZAVALIA, S. AMIR

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Abstract: Circadian clocks generate rhythms ranging from the molecular to the organism level which is believed to be essential in order to provide optimal function of the biological system in

a daily changing environment. Indeed, disruption of circadian clocks on an organism as well as tissue-specific level is associated with a wide range of chronic health problems in humans such as the incidence of mental disorders, emphasizing their clinical relevance. The circadian clock in medium spiny neurons (MSNs) of the striatum is of great interest given the fact that this brain region is associated with mood- and anxiety-related conditions, raising the question if a disruption of the circadian clock may alter these processes and contribute to the incidence of neuropsychiatric disorders. To investigate the role of a functional circadian clock in the striatum, conditional Bmal1 knockouts were generated by crossing C57BJ/6 mice homozygous for floxed alleles of the Bmal1 locus with C57BJ/6 mice expressing Cre under the control of the Gpr88 promoter. The knockout is confirmed by mRNA expression analysis of the Bmal1 floxed locus in homo- and heterozygote mice compared to homozygote wild type (WT) littermates. Further examination by immunohistochemical staining and Western blotting demonstrates that expression of Bmal1 is disabled in striatal MSNs of knockout mice exclusively. Strikingly, mRNA expression of circadian clock and clock-controlled genes is altered in Bmal1 knockouts compared to control animals at various time points, indicating that circadian clock function is disrupted in mice lacking a functional copy of Bmal1 in MSNs. Subsequently, homo- and heterozygote knockout mice and WT littermate controls were tested to assess the impact of the Bmal1 knockout in striatal MSNs on behaviour with focus on circadian as well as mood- and anxiety-related phenotypes. Whereas various parameters of daily locomotor activity rhythms are similar in Bmal1 knockouts compared to control mice, it is shown that Bmal1 knockout animals display higher levels of locomotor activity, tend to spend less time in the center of an open field arena and display increased thigmotactic behaviour in an open field test compared to control mice. Shorter immobility time is observed in Bmal1 knockout mice compared to control counterparts in a tail suspension test. The results of the current study indicate that loss of the circadian clock gene Bmal1 in the striatum appears to be involved in the incidence of anxiety-related conditions and hyperactivity in novel environments, however, further studies need to be conducted in order to draw final conclusions.

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Poster

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Title: Serotonergic modulation of basolateral amygdala neurons mediates anxiety-related behaviors

Authors: *Y. XIAODAN^{1,2}, C.-J. SHEN², J.-Y. FU², H.-Y. LAI^{1,2}, X.-M. LI²

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Abstract: Anxiety, an emotional response to distal perceived threats, is thought to be regulated by the serotonin (5-HT) system and the amygdala traditionally. However, it remains unclear how the 5-HT transmission modulates neuronal activity in the amygdala to mediate anxiety. Here, we found that optogenetically manipulation of the serotonergic inputs onto the basolateral amygdala (BLA) bilaterally regulated anxiety state in a frequency dependent manner, via different subtypes of serotonin receptors in the pyramidal neurons and the GABAergic neurons. Our study illuminates the mechanisms of how 5HT changes the BLA activity to attenuate anxiety state, and provides a potential therapeutic target of selective serotonin reuptake inhibitors (SSRIs) in patients with anxiety disorders.

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Poster

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Program #/Poster #: 078.09/AAA21

Topic: G.03. Emotion

Title: Arachidonoyl serotonin (aa-5-HT) modulates general fear-like behavior and inhibits mesolimbic dopamine release

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Abstract: Cannabinergic and vanilloidergic signaling are mechanisms of interest for the treatment of anxiety symptoms because of the anxiolytic properties of cannabinoid type 1 receptor (CB₁R) activation and transient potential vanilloid type 1 channel (TRPV₁) inhibition. Arachidonoyl serotonin (AA-5-HT), a dual fatty acid amide hydrolase and TRPV₁ inhibitor provides an efficient means of modulating these systems. We therefore examined the effects of AA-5-HT on anxiety- and fear-like behaviors in male low (C57BL/6J; [B6]) and high (BALB/cJ; [BCJ]) anxiety mice in light/dark box (LDB), open-field (OF), and fear extinction (FE) paradigms. AA-5-HT (1 mg/kg) administration did not affect anxiety-related behaviors in the LDB or OF in B6 mice. However, AA-5-HT treatment attenuated generalized fear compared to

vehicle treated B6s. AA-5-HT administration increased rearing and locomotion in the LDB in BCJ mice but did not affect other fear-related behaviors. *In vivo* fixed potential amperometry was used to determine the effects of AA-5-HT on phasic dopamine release in the basolateral amygdala (BLA) and nucleus accumbens (NAc) of mice. AA-5-HT inhibited phasic dopamine release in the BLA of BCJs and the NAc of B6s. Our results suggest that contextual factors interact with basal anxiety levels to modulate the effects of cannabinergic signaling on fear-related behaviors. We also provide evidence of cannabinergic and dopaminergic interactions in the BLA which could affect anxiety and fear. The absence of elevated subsecond dopamine release in the NAc following systemic AA-5-HT administration suggests that the drug may not produce any rewarding effects. Ultimately, our findings imply that the utility of AA-5-HT as an anxiolytic drug may be limited by individual differences in contextual factors and basal anxiety symptoms in humans.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: NNSFC Grant 91632304

Title: Auditory cortex-driven disinhibition of GABA_BR signaling in amygdala mediates fear renewal

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Abstract: Fear renewal refers to the context-specific relapse of extinguished fear and represents a prevailing model of post-traumatic stress disorder; however, the circuits and their underlying mechanisms remain largely unknown. Here we find that renewal-inducing stimuli enhanced the excitability of pyramidal neurons in LA and excitatory synaptic inputs from auditory cortex to LA in fear-extinguished mice. Mechanistically, activation of the presynaptic GABA_B receptor reversed renewal-induced increase of excitatory synaptic inputs to LA, and intra-LA activation of this signaling cascade also attenuated fear renewal. Moreover, inactivating the auditory inputs to LA prevents fear renewal in the conditioning context, while activating this pathway during auditory conditioned stimulus (CS) ectopically evoked fear responses in the extinction training. Together, these results reveal that GABA_B receptor in the projection from auditory cortex to LA

gate contextual-specific retrieval of cued fear memory *via* modulating action of the long-range corticoamygdalar excitability.

Disclosures:

Poster

078. Emotion: Fear, Anxiety, and Pain II

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

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Topic: G.03. Emotion

Title: Modality-specific innate fear neurons in basolateral amygdala

Authors: *J. LIU¹, L. LIN², D. V. WANG³

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Abstract: Fear, as a basic emotion, activates related neural circuits for avoiding threats, which is essential for survival and normal life. Extensive studies have focused on the neural mechanism underlying the learned/conditioned fear. However, the neuronal activities and circuitry of the innate/unconditioned fear have not yet been systematically studied. Converging evidence suggests that the amygdala is a key brain region involved in both learned and innate fear. Employing a classical tone-footshock conditioning procedure in mice, we found that only a small fraction of the basolateral amygdala (BLA) neurons responded to the conditioned tone. Therefore, we designed new behavioral paradigms to test the BLA neuronal responsiveness to a variety of unconditioned fearful stimuli, measuring physiological markers (heart rate and heart rate variability) and behavioral scores (freezing) to identify the fearful states. In a first set of experiments, preliminary results showed individual BLA neurons preferentially responding to loud sound (auditory), moving object (visual), cat odor (olfactory), high place exposure (likely vestibular), or other stimuli. Most of the above fear-related neurons, termed ‘BLA innate fear neurons’, exhibited highly modality-specific responses, suggesting that these fear neurons involve distinct neural circuits. Importantly, these BLA innate fear neurons display long-lasting sustained activity (up to minutes) even after the termination of the stimuli, indicating that their activity is mediated by inputs beyond primary sensory inputs. Previous studies have demonstrated that the hippocampal/parahippocampal region and prefrontal cortex play a pivotal role in fear. To identify regulatory afferents that either activate or inhibit the firing of the BLA innate fear neurons, we injected Channelrhodopsin-2 (ChR2) viruses in major BLA-projecting regions, including the Hipp/Parahipp and PFC. Then, we implanted an optrode (an optical fiber surrounded by eight tetrodes) into the BLA to examine how photoactivation of these afferents may potentially affect innate fear neuronal activities and innate fear levels. Preliminary results revealed that a subpopulation of BLA neurons can be activated upon photostimulation of the

PFC-to-BLA afferents. Furthermore, the Hipp/Parahipp-to-BLA afferents can activate or inhibit distinct subpopulations of BLA neurons. A demonstration of specific projections to BLA regulating levels of innate fear could have clinical implications for treatment of excessive fear and anxiety disorders.

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Poster

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Title: Contextual fear memory formation promotes psd-95 phosphorylation and modulates ampar subunits differentially between adult and juvenile rats

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Abstract: It is well known that young organisms do not maintain memories as long as adults, but the mechanisms for this ontogenetic difference are unknown. Our overall research is to identify the behavioral and molecular mechanisms of these ontogenetic differences. Previous work has revealed that the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) subunits are trafficked into the synaptic membrane following spatial-memory retrieval.

Additionally, phosphorylated PSD-95 (pS295) promotes AMPAR stabilization at the synapse. Rats were assigned to either pedestal stress (1h) or no stress control (home cage). All animals were placed in an open field for 5 min at the base of a 6x6 sq inch pedestal (4ft high). Stress subjects were then placed on this pedestal for 1hr and control subjects were placed in their home cage following initial exploration. All animals returned to the open field for 5 min either 1d or 7d following initial exposure. Behavioral recordings were then analyzed for time in a freeze posture (sec). 24h memory retrieval test shows adult (P90) and juvenile (P26) stress rats increase their freezing time compared to controls. However, the 7d memory retrieval test shows, P90 stress rats but not the P26 stress rats freeze while in the fear context. Twenty minutes after the memory retrieval test, hippocampi and amygdala were micro dissected and prepared for western blot analysis. Our results show that 24h fear memory retrieval induced an upregulation of PSD95 and pS295 in the adult amygdala but not in the juvenile. However, the juvenile animals upregulated PKM ζ and GluA2/3 in the DH but not the adults. Following the 7d memory retrieval test, Adults upregulated GluA2 in the amygdala but not the juveniles. In the DH, adults increased PSD95 and

pS295 but not the juveniles. These results suggest that adult fear memory formation involves the sequential activation of the amygdala-hippocampal pathway, involving the stabilization of AMPA receptors through increased phosphorylation of PSD95 (pS295). Conversely, juvenile contextual fear memory (lasting less than 7d) does not engage amygdala activity, but selectively increases GluA2/3 and PKM ζ within the DH by 24h. Our data overall illustrate the longevity of this fear-based memory in adults, but the instability of memory retention in juveniles; suggesting this pattern of plastic changes could be pivotal during development.

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Poster

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Title: Noradrenergic signaling in the central nucleus of amygdala mediates learning independent behavioral fear expression

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Abstract: Our previous report showed that optogenetic activation of noradrenergic neurons in locus coeruleus (NA^{LC} neurons) projecting to lateral amygdala (LA)(NA^{LC}→LA pathway) evoked robust freezing behavior against similar cues or contexts with ones that are not paired with aversive electric shock in conditioning period. This suggests that NA^{LC}→LA pathway plays an important role in fear generalization. The freezing was not induced in naïve mice (mice without any prior conditioning), or in the home cage condition even in mice with prior conditioning procedure. Recent studies revealed the diverse input/output architecture of NA^{LC} neurons suggesting functional heterogeneity of NA^{LC} neurons depending on their diverse projection pathways. It is well known that NA^{LC} neurons especially projecting to the LA strengthen the synaptic plasticity to play an important role for consolidating fear memory. However, the role of NA^{LC} neurons projecting to the CeA in fear memory processing has not been well recognized, although there is high density of NA axonal innervation in the region. We utilized *NAT-Cre* mice in which Cre recombinase is specifically expressed in the NA^{LC} neurons for anterograde tracing with Cre-dependent AAV expressing ChR2 (AAV-FLEX-ChR2). We found NA^{LC} neurons send dense axonal projections to the CeA compared to the adjacent LA region. To assess the role of

NA^{LC→CeA} pathway, we injected Cre-dependent retrograde AAV expressing Chr2 into the CeA (AAVretro-FLEX-ChR2) and implanted optic fiber at the LC. Optogenetic stimulation of NA^{LC→CeA} pathway induced robust freezing behavior in any kind of context without prior fear conditioning, contrasting with the observation that optogenetic excitation of NA^{LC→LA} pathway didn't show any freezing without conditioning. 20 s stimulation of NA^{LC→CeA} pathway showed significant decrease in total distance and time duration in the center using open field test. Using Pavlovian fear conditioning paradigm, 5 times 30 s auditory CS presentation following optogenetic stimulation for 2 s gradually increased freezing behavior in context A. However, after 24 h, CS presentation in similar but distinct context (context A') or being exposed to the same context (context A) didn't show any freezing behavior suggesting that NA^{LC→CeA} pathway is not involved in the fear memory consolidation. Finally, retrograde tracing with different retrobeads injected into the CeA and LA showed that distinct population of NA^{LC} neurons might project to the CeA and LA. These results suggest that differential populations of NA^{LC} neurons projecting to the CeA and LA regulate learning independent and dependent behavioral fear expression, respectively.

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Poster

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University of Colorado Denver CRISP Award

Title: Social fear conditioning in differentially housed adolescent rats exposed to the escapable social interaction test

Authors: *L. M. DAWUD¹, E. C. LOETZ², K. POPPLETON², I. MAMAYAN¹, B. N. GREENWOOD², S. T. BLAND²

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Abstract: Social fear is a learned behavior and can be adaptive; however, heightened social fear is frequently a component of stress-related disorders. Individual differences in vulnerability to learned social fear may be critical in the development of stress-related disorders. Post-weaning social isolation (PSI) is a model of early life adversity that consists of housing rats in isolation during the critical period of adolescence, in contrast with social rearing (SR). PSI alters social behavior and may increase vulnerability to an aversive social event. We have developed a novel social fear conditioning procedure in rats using a modified standard conditioning chamber in

which a footshock is paired with exposure to a stimulus rat (contained in a special insert) that does not receive a footshock; social behavior is tested the next day in a different context. We have previously shown that after social fear conditioning, PSI male and female rats had increased escape behavior compared to SR rats and controls when re-exposed to the stimulus rat in a novel open field. Here, we further investigated this apparent increase in escape behavior by combining social fear conditioning with an automated escapable social interaction test (ESIT). The ESIT consists of a social interaction chamber containing a tethered stimulus rat and a door leading to an escape chamber. On Day 1, male Sprague Dawley rats were exposed to 4 footshocks paired with a novel stimulus rat (social fear conditioning), whereas the 3 control groups were exposed to either a stimulus rat only, foot shocks only, or context only. On Days 2 and 3, all rats were exposed to the ESIT for 10 minutes with the same stimulus rat from day 1 tethered in the social interaction chamber. Anymaze software recorded the time spent in the escape chamber and latency to exit the escape chamber. Male rats (we will also report results from females) exposed to social fear conditioning displayed a significant increase in latency to interact compared with rats exposed to the social stimulus only. Exposure to social fear conditioning also significantly increased time spent in the escape chamber compared to rats only exposed to social stimulus. There was no significant effect of history of social isolation. Rats exposed to social fear conditioning display increased escape behavior when re-exposed to the same stimulus rat the next day in a quantifiable escapable social interaction test.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

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Topic: G.03. Emotion

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Title: Naltrexone administration during extended fear conditioning prevents low pre-incubated fear in the fear incubation model

Authors: *A. PAJSER, C. FOSTER, A. WESTON, C. L. PICKENS
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Abstract: Previous research has shown that extended fear conditioning leads to initially low fear that grows over time, often termed fear incubation. This is contrary to the pattern seen after limited fear conditioning, which results in high fear initially that is sustained over time. The neurobiological basis of these differences is unknown. One possibility is that endogenous opiates

are released over the course of extended training, decreasing sensitivity to the fear-inducing stimulus. This could lead to the conditioned cues being associated with an ineffective shock, causing decreased fear. The current study was designed to investigate this possibility by blocking endogenous opiate activity during fear training via naltrexone administration. Male Long-Evans rats (n=8-12/group) acquired lever-pressing and then underwent training. During these training sessions, the rats experienced 10 30-sec tones pseudo-randomly throughout the 90-min session, with some groups experiencing the tones co-terminating with a 0.5-sec foot-shock. There were 5 groups of experimental subjects. One group received 1 day of training with tone-shock pairings. Four other groups received 10 days of training with tone presentation, with 2 groups receiving tones alone and 2 groups receiving tones paired with shocks. Crossed with tone or tone-shock designation, two groups received injections of naltrexone (7 mg/kg, s.c.) before training days 2-10, and two groups received saline injections on these days. The day after fear conditioning was completed, animals underwent a contextual fear test, and the following day they underwent a cued fear test. After one month of incubation, animals underwent a contextual fear test again, and a cued fear test the following day. No injections were given before the tests. Fear was measured using with conditioned suppression of lever-pressing. We found that the group given 10 tone-shock sessions + 9 saline injections showed the pattern of behavior typically seen across the course of training in the extended training fear incubation paradigm: fear that decreases across training with low fear in the day 2 test that increased when tested one month later. However, the corresponding naltrexone group did not show the same decrease in fear across training, and fear was high in the day 2 test and remained steady at the 1 month test, similar to the pattern seen in group given 1 day of training. This suggests that the neurobiological basis behind the extended training fear incubation paradigm may be the release of endogenous opioids that develops throughout the course of training.

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Poster

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Title: Optogenetic reactivation of socially-labeled cells modulates fear but has limited effects on conflict anxiety

Authors: K. AHUNA¹, V. GUTZEIT², A. CUNNINGHAM¹, M. O. WORONIECKA¹, M. ROONEY³, T. SANTOS³, C. A. DENNY⁴, *Z. R. DONALDSON⁵

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Abstract: Amongst social animals, the presence of a conspecific companion can have powerful effects on mood and behavior. In particular, the social modulation of fear and anxiety represents a highly conserved trait, as both humans and rodents display decreases in anxiety and stress responses when an affiliative conspecific is present. However, the neural processes underlying this behavioral phenomenon remain largely unknown. Our group has found that in mice, conspecific presence decreases freezing in both conditioned and innate fearful contexts, but does not increase exploration in innately anxiogenic contexts. In order to identify neuronal populations that may contribute to social buffering of fear and anxiety responses, we used a mouse line in which *Arc*-expressing neurons are indelibly labeled following interaction with a novel conspecific. We identified a subset of cells within the infralimbic prefrontal cortex (ILPFC) of male and female *ArcCreER^{T2}* mice that are labeled in response to interacting with a novel, ovariectomized female conspecific, but not in response to a toy mouse, novel object, or food reward. Optogenetic reactivation of conspecific-labeled ChR2-eYFP⁺ neurons was found to modulate fear-associated freezing, without impacting locomotion. Optogenetic reactivation did not affect exploration of anxiogenic environments or appear to be rewarding. Together, these studies will elucidate if activation of neurons associated with an affiliative conspecific in the ILPFC is sufficient to mediate the effects of conspecific presence on fear or anxiety responses. Subsequently, targeting this cell population may provide novel therapeutic opportunities that harness circuits naturally engaged by social interaction to treat fear and anxiety-related disorders.

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Poster

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ANR-11- IDEX-0001-02 PSL* Research University

Title: Frequency specific tuning of prefrontal cortex to fear-related breathing regulates emotional expression

Authors: *S. BAGUR¹, J. M. LEFORT², M. M. LACROIX², G. DE LAVILLEON², C. HERRY³, H. GEOFFROY², K. BENCHENANE²

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Abstract: Interoceptive theories of emotions have been core to their study since the dawn of psychology. However, the physiological basis of the tight link between emotions and somatic changes and whether these emotional peripheral responses have any direct impact on the brain related to a functional role remain open questions. Here we show that respiration rhythm is an excellent somatic marker of fear in mice which is co-opted by the prefrontal cortex to play a key role in freezing behavior. By using cue fear conditioning, we demonstrate that the 4Hz oscillation observed in the prefrontal cortex (PFC) during freezing comes from breathing, transmitted via the olfactory bulb (OB). This oscillation modulates PFC neuronal activity most strongly during freezing. Optogenetic manipulation reveals that transmission of oscillatory inputs from the OB to the PFC peaks at 4Hz and is almost blocked at 10Hz suggesting a frequency-dependent gating mechanism for communication between brain areas. Finally, the breathing-related 4Hz oscillation plays a causal role in the expression of fear since both bullectomy and optogenetic perturbation reduce freezing levels. This suggests that breathing control for emotional regulation could be due to a direct modulation of brain activity.

Together these results propose a mechanistic model for a brain-body-brain loop in which the expression of emotional behaviour engenders somatic changes which then feedback to the brain to participate in sustaining emotional states.

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Poster

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Topic: G.03. Emotion

Support: DA041482

DA043184

Title: Control of anxiety-like behavior and fear learning by serotonergic circuits innervating the interpeduncular nucleus

Authors: *I.-J. YOU¹, L. LIU², A. SACINO¹, M. UCHIGASHIMA³, K. FUTAI¹, A. R. TAPPER¹

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Abstract: Recently, the interpeduncular nucleus (IPN) has been implicated as a critical neuroanatomical substrate for modulating fear and anxiety-like behavior. However, functional IPN afferent and efferent circuitry that contributes to these behaviors is largely unknown. Interestingly, viral tracing studies indicate that the IPN receives projections from the medial raphe nucleus (MRN), although serotonergic signaling in the IPN and the functional relevance of this MRN→IPN input has not been elucidated. Molecular and biophysical analysis of 5-HT receptors in the IPN indicated robust functional expression of 5-HT_{1A}, but not 5-HT₅ receptors. Double fluorescent in situ hybridization experiments revealed co-localization of 5-HT_{1A} receptor with tryptophan hydroxylase₂ and glutamic acid decarboxylase ₆₇ transcripts suggesting serotonergic IPN inputs may innervate both serotonergic and GABAergic neurons in the rostral sub-nuclei of the IPN. To test the hypothesis that MRN→IPN serotonergic inputs contribute to anxiety-like behavior and fear learning, we expressed channelrhodopsin or halorhodopsin in MRN serotonergic neurons that project to the IPN using retrograde viral delivery in FEV-Cre mice. Optical stimulation of serotonergic terminals in the IPN increased anxiety-like behavior in the elevated plus maze and open field test. In contrast, optical inhibition of MRN→IPN inputs did not significantly affect anxiety-like behaviors suggesting that this circuit is not engaged during baseline anxiety behavior. However, optical inhibition of MRN→IPN inputs reduced the acquisition of fear conditioning. These results reveal a novel role for a serotonergic MRN→IPN circuit in modulating anxiety-like behavior and fear learning.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: MH093981

DA09082

MH093981

Title: Social stress activates amygdalar corticotropin releasing factor and brainstem enkephalinergic afferents to the rat locus coeruleus in adolescent rats depending on coping strategy

Authors: *Y. SHI¹, B. A. S. REYES¹, E. J. VAN BOCKSTAELE¹, X.-Y. ZHANG², S. LUZ², S. BHATNAGAR²

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Abstract: Stress-related psychiatric disorders affect both men and women. Stress is a critical factor affecting mental health and can have long lasting effects on the brain and behavior. The timing of stress exposure influences the effects of stress on the brain. Adolescence is characterized by increased neuronal plasticity rendering this period vulnerable to stress. A common stressor encountered during this period is social stress. An ethologically relevant animal model of social stress is the resident-intruder model. Using this model, we have shown that social stress engages distinct amygdalar corticotropin-releasing factor (CRF)- and nucleus paragigantocellularis (PGi) opioid-containing afferents to the locus coeruleus (LC) in adult male and female rats, that segregate according to coping strategy as determined by the latency of the rats to assume a defeat posture. Here, we identified the neural circuitry that activates the LC following social stress in adolescent male and female Sprague-Dawley rats. Prior to social defeat exposure, rats were injected with the retrograde tracer, Fluorogold (FG) into the LC. Three days following FG injection, rats were subjected to repeated (5 days) social defeat or control manipulation, and perfused 90 minutes after the last session. Sections through the lower brainstem and forebrain were collected and processed for immunocytochemical detection of c-fos, a marker of neuronal activity, FG and CRF or enkephalin (ENK). Consistent with our previous tracing studies, retrogradely labeled neurons from the LC were distributed throughout the rostral-caudal segments of the central nucleus of the amygdala (CeA) and PGi. Statistical analysis showed that c-fos expression in the CeA was significantly increased in the short latency to defeat (SL) rats ($P < 0.01$) when compared to control and LL latency (LL) in both male and female rats. Triple labeling of c-fos, FG and CRF revealed significant increases in the number of c-fos, FG and CRF-immunoreactive neurons in the CeA of SL rats ($P < 0.05$) when compared to control and LL in both male and female rats. In the PGi, significant increases were observed in the number of c-fos, FG and ENK-immunoreactive neurons of LL ($P < 0.05$) rats when compared to control and SL in both male and female subjects. These results show that social stress differentially engages the LC depending on coping strategy in both male and female adolescent rats and that such distinctions in neural circuit activation may translate to diverse behavioral and physiological consequences.

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Poster

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Title: Behavioral and histological phenotypes of calyntenin triple knock out mice

Authors: ***K. MORI**, M. KOEBIS, Y. KIYAMA, T. MANABE, A. AIBA, Y. IINO
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Abstract: Calyntenins are members of the cadherin superfamily and are expressed in the central nervous system. This molecule is conserved through animal kingdom. For example, *C. elegans* has one homolog and mammals have three homologs. Our lab previously found that calyntenin/CASY-1 in *C. elegans* transports an insulin-like receptor to the axon and this localization regulates synaptic activity which is assumed to generate memory-dependent behaviors. In mammals, although several reports have suggested that calyntenins function in synapse formation, axonal transport and memory formation, much remains unknown about the roles of these proteins, especially at the organismal level. Mammalian calyntenins are coded for by three paralogous genes and are likely to have functional redundancies. To reveal their functions at the organismal level, we generated triple knockout (TKO) mice by using the CRISPR/Cas9 system. We are currently characterizing the phenotypes of the TKO mice via histological, physiological and behavioral analyses. From the histological analyses, we found that calyntenin TKO mice have fewer inhibitory neurons in several brain regions, which is consistent with the phenotype of the calyntenin-2 KO mice. At the behavioral level, we performed the behavioral battery test and found that calyntenin TKO mice show several mental disorder-like phenotypes. This mice also showed the abnormal response to stress. We are currently looking at the detail of this phenotype and also the relationships between the histological, physiological and behavioral phenotypes.

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Poster

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Topic: G.03. Emotion

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Title: Active defensive behavior driven by the Lateral Hypothalamus to the midbrain periaqueductal gray glutamatergic neuron activation

Authors: *P. WEN¹, L. XU³, Y. QIU³, X. ZHU², L. WANG², X. HE², L. YANG², J. WANG², Z. ZHANG², F. XU²

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Abstract: The active defensive behavior is one of the critical strategies for animals to survive the dangerous environment and win the evolution race. However, the neural mechanisms are poorly understood. Here, we developed a sound-induced innate flight response model in mice and found that c-fos expression in the LH was significantly enhanced. Then, revealed by rabies trans-synaptic retrograde tracing, it was shown that the glutamatergic neurons in the PAG, which are critical for defensive response, were directly innervated by LH neurons. In the present study, we found that optogenetic activation of the lateral hypothalamus (LH) glutamatergic axonal projections in the periaqueductal gray (PAG) is aversion, and could produce fear-like flight behaviors. Further studies showed that activating this pathway at different foraging stage could diversely regulate the feeding and escaping choices in food restricted mice. Our studies revealed a neural projection from the LH to the PAG mediating the active defensive behavior, which could diversely influence dietary behavior.

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Poster

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Topic: G.03. Emotion

Support: Deutsche Forschungsgemeinschaft (DFG, SFB779/B13)

Title: Predator odor induced 22-kHz ultrasonic vocalizations in rats: Effects on defensive behaviors in conspecifics upon replay

Authors: *M. WÖHR¹, M. BROSCHE², K. E. A. WERNECKE², M. WILLADSEN¹, M. FENDT²

¹Philipps-University of Marburg, Marburg, Germany; ²Otto-von-Guericke Univ. Magdeburg, Magdeburg, Germany

Abstract: Predator odors often induce defensive behavior in prey animals. In rats, defensive behavior includes the emission of 22-kHz ultrasonic vocalizations (USV) and it is widely believed that 22-kHz USV serve as alarm calls to warn conspecifics about external danger. The hypothesis that 22-kHz USV have an alarming function is supported by the observation that they induce a distinct pattern of brain activation associated with anxiety and fear regulation. For instance, prominent activation in response to 22-kHz USV was repeatedly observed in the amygdala and the periaqueductal gray. The present study investigated (1) whether laboratory rats exposed to predator odors emit 22-kHz USV and (2) whether playback of such 22-kHz USV induces defensive behavior in conspecifics. To this aim, Sprague-Dawley rats were exposed to samples of fox and lion urine as well as to the synthetic predator odor TMT. Despite that all odors induced defensive behavior, only predator urine samples were able to induce 22-kHz USV in a few rats. In a second experiment, naive rats were exposed to playback presentations of the 22-kHz USV recorded in the first experiment as well as to phase-scrambled and frequency-shifted control stimuli. Low intensity playback led to a reduction in locomotor activity specifically during 22-kHz USV presentation. Under high intensity conditions, however, this effect was less specific and behavioral inhibition was also seen in response to control stimuli. Taken together, the present findings show that natural predator odors are able to induce 22-kHz USV in rats and support the hypothesis that 22-kHz USV have an alarming function.

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Poster

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Title: Intra-amygdaloid administration of the D₁ antagonist SCH23390 during exposure to a live predator and to a predator-associated context

Authors: *E. N. LEVARIO RAMÍREZ¹, M. CRESPO RAMÍREZ¹, K. FUXE², M. PÉREZ DE LA MORA¹

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Abstract: The mesoamygdaloid dopaminergic system participates in the modulation of conditioned and non-conditioned fear responses. Behaviorally, the intra-amygdaloid infusion of DA D₁ agonists and antagonists elicits anxiogenic and anxiolytic effects respectively on conditioned and non-conditioned models of fear/anxiety suggesting an anxiogenic role for the amygdaloid DA D₁ receptors. However, these studies have been restricted to relatively simple and ethologically-poor models. The aim of this study was to evaluate the role of amygdaloid DA D₁ receptors on fear responses elicited by a natural threat like predator exposure and to a predator-associated context. Adult male Wistar rats were exposed to a live cat in a rectangular plexiglass box having a safe and a danger zone relative to either the presence or absence of the cat separated by a narrow tunnel. The testing procedure consisted of three 10 min video-recorded phases. At the first phase (habituation) rats were allowed to explore the box for 4 days in the absence of any cat. Behavior at the fourth day of habituation was taken as baseline. At the second phase (acquisition), rats received a bilateral intra-amygdaloid injection of either SCH23390 (40 or 120 ng/side), a D₁ antagonist or vehicle (saline) and were immediately placed in the safe zone of the box allowing them to explore the whole device, including the danger zone where the cat was already present. Similarly, at the third phase (retrieval), one day after cat exposure, rats were microinfused with the same doses of SCH23390 into the amygdala and immediately they were exposed to a predator-associated context (the same box but without any cat). Results showed that saline treated rats avoid exploring the danger zone of the box (avoidance behavior) when they are exposed to the cat. Intra-amygdaloid administration of SCH23390 has no effects on the time spent by the rats in the danger zone during the acquisition of the avoidance behavior but selectively increased the time spent in this zone at the higher dose (120 ng/side) following retrieval of the behavior 24 hours after the exposure to the cat. Our results suggest that amygdaloid DA D₁ receptor mechanisms may have a role in the aversive behavior that rats experience when they are confronted with natural threats.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: DFG MA 4692/3-2

Title: Does a decrease of excitation/inhibition balance in the infralimbic region of the prefrontal cortex influence anxiety behavior?

Authors: *L. BERG, A. STAMBULACHIS, O. A. MASSECK
Advanced Fluorescence Microscopy, Ruhr Univ. Bochum, Bochum, Germany

Abstract: Dysbalance of excitation and inhibition within the prefrontal cortex is associated with severe psychiatric diseases, whereby an increase in E/I ratios is associated with social and cognitive deficits. In a previous study we already demonstrate with optogenetic methods, that an imbalance of E/I in the infralimbic region of the prefrontal cortex increased anxiety. We now hypothesize that inhibition, i.e. shifting E/I to inhibition, will reduce anxiety. To test our hypothesis we specifically expressed an inhibitory optogenetic tool, ArchT in pyramidal neurons of the infralimbic cortex. We performed three well-established anxiety tests, the openfield, elevated plus maze and the novelty suppressed feeding test. None of our performed behavioral tests could show an influence of pyramidal neuron inhibition, i.e. shifting E/I balance to inhibition, on anxiety. Also motor performance and feeding behavior were unaffected by pyramidal neuron inhibition. Analyses of the activity marker c-fos in the IL revealed inhibition of pyramidal neurons and a shift in the E/I during light stimulation. Taken together our results indicate that a reduction in E/I has no influence on anxiety behavior. Overall our study improves our knowledge about complex cortical mechanism of anxiety.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: NIH DA035371

Title: Do α 3-containing nicotinic acetylcholine receptors (nAChRs) modulate anxiety behavior?

Authors: *C. SMITH, A. R. TAPPER, P. D. GARDNER
Neurobio., Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: More than 260 million people suffer from anxiety disorder, thus it is important to understand the molecular mechanisms underlying this mental health disorder. Studies showed that nicotinic acetylcholine receptors (nAChRs) play a role in anxiety-related behaviors. nAChRs are ligand-gated cation channels that bind the endogenous neurotransmitter acetylcholine for activation. There are eleven mammalian neuronal nAChR subunits, α 2- α 7, α 9, α 10 and β 2- β 4, which are encoded by the *CHRNA2-CHRNA7*, *CHRNA9*, *CHRNA10*, and *CHRNA2-B4* genes, respectively. These subunits co-assemble to form functional homopentamers or heteropentamers consisting of various combinations of alpha and beta subunits. nAChRs are highly expressed in the habenulo-interpeduncular pathway, a brain circuit that is involved with negative emotional state. Interestingly, knockout studies of the α 5 and β 4 nAChR subunits, which are tightly clustered and co-regulated with the α 3 nAChR subunit, play a role in anxiety-related behaviors. However, little is known regarding the physiological relevance of α 3-containing nAChRs in anxiogenic behaviors due to α 3 nAChR subunit knockout mice being inviable shortly after birth. The α 3 nAChR subunit is highly expressed in the habenulo-interpeduncular pathway, suggesting a role for this subunit in anxiety. Thus, I plan to test the physiological relevance of α 3-containing nAChRs in anxiety-related behaviors by knocking down α 3 nAChR subunit expression in the medial habenula (MHb) or interpeduncular nucleus (IPN) and subsequently testing for anxiogenic behaviors. Using a viral-mediated shRNA approach, I achieved an approximately 80% knockdown of *Chrna3* expression *in vitro* (Neuro2A cells). To determine whether α 3-containing nAChRs are involved in anxiety-related behaviors, I injected viral particles expressing the shRNA or control virus into the IPN of 20, 6-week old C57BL/6J male mice. Five weeks post-injection, I performed the open field test (OFT), elevated plus maze (EPM), and marble burying test (MBT). There was a trend of increased anxiety in α 3 nAChR subunit knockdown mice in the OFT and EPM, suggesting that α 3-containing nAChRs modulate anxiogenic behaviors.

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Poster

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Program #/Poster #: 078.26/BBB12

Topic: G.03. Emotion

Title: Sex and threat certainty differentially modulate ultrasonic and locomotor behavioral expressions of fear and anxiety

Authors: J. O. TAYLOR¹, J. R. PETERSON², V. TASKOV³, M. WHITTINGTON³, B. VO³, G. MONSON¹, S. LIPINSKA¹, E. NYAM-OCHIR¹, C. M. URBANO³, *B. G. COOPER³
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Abstract: In the United States, 40% of United States adults will suffer from an anxiety disorder, and women are more likely than men to develop affective disorders. Animal models are essential for improving our understanding of the etiology and treatment of emotional disorders, yet the majority of rodent studies only examine males. Laboratory rats produce a specific subtype of 50 kHz vocalization (CF 50kHz) when exposed to an initial stressor and then begin to produce 22 kHz calls during sustained threat. This suggests that vocal patterns indicate intensity of negative affective state and may discriminate between anxiety and fear. We investigated sex differences in a contextual fear conditioning paradigm that rapidly shifts animals between differing emotional states. Intensity of negative affective state was manipulated by delivering sequences of either temporally unpredictable or predictable mild footshocks (0.5 mA, 0.5 s) in a contextual fear conditioning chamber; unpredictable and predictable threats should elicit anxiety and fear, respectively. Intensity of negative affective state was measured during training and on two subsequent test days via locomotor responses related to anxiety (rearing) and fear (freezing) and vocal behavior (ultrasonic vocalizations). During training, there were no significant sex or threat predictability differences in locomotor behaviors, but male rats were more likely to produce 22 kHz calls (90%), whereas only 50% of female rats produced 22 kHz calls. During contextual fear memory test, female rats engaged in more rearing behavior than males, freezing was more pronounced in the unpredictable footshock condition, and few animals produced vocalizations. After a single reinstatement footshock, male rats exhibited enhanced freezing behavior compared to females. Male rats also produced 22 kHz ultrasonic vocalizations (60%), whereas none of the females produced 22 kHz calls. In contrast, female rats were more likely to produce 50 kHz vocalizations before and after footshock. These results show that sex and threat predictability differentially modulate locomotor and vocal behaviors. Male rats exhibit enhanced fear conditioning memory, and produce more 22 kHz calls than females, whereas females are more likely to engage in anxiety-related behaviors (e.g., rearing) during the fear memory test and produce 50 kHz vocalizations during fear conditioning and reinstatement. These results illustrate the importance of studying sex differences in locomotor behaviors related to fear conditioning and illustrate that subtle differences in emotional state can be elucidated by measuring ultrasonic vocalizations.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 078.27/BBB13

Topic: G.03. Emotion

Support: R01 MH061933; “G protein-gated K⁺ channels and inhibitory signaling”
UMN Viral Vector and Cloning Core

Title: Activation of G protein-gated inwardly rectifying K⁺ channels in ventral hippocampus reduces anxiety-related behaviors

Authors: *B. N. VO, E. MARRON, K. WICKMAN
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Abstract: Inhibitory G protein signaling plays a critical role in the etiology and treatment of anxiety disorders. Several commonly prescribed drugs used to treat anxiety disorders enhance inhibitory G protein signaling in neurons, leading to the modulation of multiple enzymes and ion channels. The relative contributions of these G protein-regulated effectors to anxiety-related behavior are unclear. The G protein-gated inwardly rectifying K⁺ (GIRK) channel is one such effector, mediating the postsynaptic inhibitory effect of GABA and other inhibitory neurotransmitters. GIRK channels consist of various combinations of four homologous subunits (GIRK1-4). ML297 is a new and selective activator of GIRK1-containing GIRK channels, and systemic administration of ML297 reduces anxiety-related behavior in mice, without exhibiting addictive potential. The present exploratory study seeks to identify the brain region(s) where the selective activation of this GIRK channel subtype contributes to the reduction in anxiety-related behavior. We performed intracranial manipulations to deliver ML297 to two key brain regions implicated in anxiety: the ventral hippocampus (vHPC) and the basolateral amygdala (BLA). We assessed the impact of these manipulations on anxiety-related behavior using the elevated plus maze (EPM). Male mice, ~ 50 d at the time of surgery and ~ 70-80 d at the end of behavior (sample sizes: 8-10 mice/group), are used in this study. We find that ML297 infusion into the vHPC reduces anxiety-related behavior in the EPM test, suggesting vHPC as a candidate brain region exerting the anxiolytic effects observed with systemic administration of ML297. Conversely, intra-BLA ML297 did not impact EPM performance. Next, we employed a complementary chemogenetic approach, allowing for the manipulation of a specific neuronal subtype in the vHPC. We started by investigating pyramidal neurons in the vCA1 (a sub-region of the vHPC). We expressed a Cre-dependent inhibitory DREADD (Designer Receptors Exclusively Activated by Designer Drugs) in the vCA1 of CaMKII α -Cre mice (male and female, same age, group sizes as above). We find that inhibition of vCA1 pyramidal neurons reduces anxiety-related behavior in the EPM. Collectively, our data provide insights into the anatomic

region and cellular details underlying the contribution of GIRK channels to anxiety-related behavior. This insight into the neural circuits and substrates underlying anxiety highlights GIRK channels as a potential therapeutic target for anxiety disorders and other relevant diseases.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 078.28/BBB14

Topic: G.03. Emotion

Support: NIDA R00-DA038725 (RA)

Title: Opposing role of kappa opioid receptors in cold and heat responsivity

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Abstract: The role of kappa opioid receptors (KOR) has been well elucidated in heat sensation, however less is known about their role in cold sensation. Studies have demonstrated that transient receptor potential (TRP) A1 channels facilitate the perception of noxious cold at the level of dorsal root ganglia (DRG), where expression of KOR has also been reported. In this study we are investigating the role of the KOR in mediating cold sensation and whether the presence/activation of TRP channels modulates such an effect. To measure heat responsivity, we used the tail flick assay. We injected male and female C57BL/6 wildtype mice (WT) with U50,488 (KOR agonist, 5 and 10 mg/kg i.p.) and calculated the latency to tail flick. To measure cold responsivity we used the cold plate and cold plantar tests. For the cold plate we habituated male WT mice in plexiglass boxes for 1 hr prior to treatment with: 1) U50 (5mg/kg, i.p.), 2) norBNI (KOR antagonist, 10mg/kg, i.p.), 3) Saline (10 ml/kg, i.p.). Post-treatment mice were placed on the cold plate for 5 minutes and nocifensive response was calculated. For the cold plantar assay, 30 mins following saline (10ml/kg) or U50 (10mg/kg) administration, we acclimated male and female WT mice on a glass plate and applied a cold stimulus to the hind-paw and measured the latency to withdraw from the cooled glass. To determine the calcium dynamics, we cultured DRG neurons from WT (male) mice and treated the cultures with a TRPA1 agonist, mustard oil (MO) (100µM), U50 (10 µM), and a combination of both at 1, 3, 5 mins respectively and quantified the change in the intensity of the Ca²⁺ indicator. The KOR agonist U50 (10mg/kg) increased tail flick response in both males and females, but was more pronounced in male mice. Mice injected with U50 showed significant potentiation in the number

of jumps on the cold plate compared to controls. U50-induced nocifensive responses were attenuated in norBNI administered mice. In the cold plantar assay, the latency to withdraw the hindpaw to cold stimulus appeared to decrease in males, but not in females. In the calcium imaging experiments, simultaneous application of MO, and U50 yielded a potentiated Ca^{2+} response, while U50 alone failed to elicit a calcium response, suggesting crosstalk between receptors. Here we show that activation of KOR increases thermal analgesia in both male and female mice, but, interestingly increases cold sensation in male mice. Further molecular, cellular, and behavioral characterization is needed to understand the contribution of KOR to physiological and pathological cold transduction and cold-triggered pain.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 078.29/CCC1

Topic: G.03. Emotion

Support: INSERM

Title: Freezing and shaking as distinct behavioural readouts of fear and anxiety

Authors: *X. LEINEKUGEL¹, M. CARREÑO-MUÑOZ¹, M. MEDRANO¹, M. MORALES NAVAS¹, M. BOMPART¹, F. MARTENS¹, P. FEUGAS¹, A. FRICK¹, M. GRANA², A. BEYELER¹

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Abstract: We recently designed a novel device (the Phenotypix) which consists in an open-field platform resting on highly sensitive piezoelectric (electro-mechanical) pressure-sensors, with which we could detect the slightest movements from freely moving rats and mice, such as individual heartbeats and breathing cycles during rest, or tremor and shaking in response to pain, fear or as motor symptoms of neurodegenerative diseases. Here, we report on the potential of this platform for the behavioural readout of fear and anxiety.

In rodents, anxiety is classically evaluated as the avoidance of innately aversive situations such as exposed or bright areas (e.g. center of an open field, open arms of a maze). Fear on the other hand, a behavioral reaction to a perceived threat, is classically quantified as freezing immobility. Using the Phenotypix to quantify freezing and shaking, we found that exposition to a novel environment induced very little freezing but significant expression of shaking during the first 10 min, which then disappeared with familiarization. Similar exposition preceded by injection of the

anxiolytic diazepam eliminated the shaking behavior without any significant effect on freezing. After a protocol of contextual fear conditioning, associating a sound with a footshock, the emission of the sound alone triggered high level of freezing but little or no shaking. In contrast, exposition to the fear-conditioned environment (in the absence of the sound) produced little freezing but high levels of shaking. A similar behavioural reaction, combining high shaking but little freezing, was produced by exposing the animal to the presence of a rat, a natural predator of the mouse.

We next investigated the behavioral effect of optogenetic activation of insular-cortex neurons projecting to the ventral hippocampus, two regions of interest in human anxiety disorders. We observed that repeated stimulations over 10 days (40 minutes in total) induced persistent shaking behaviour, while freezing response was rather phasic, only during the stimulation periods. We propose that high-frequency (80-120Hz) shaking is a sensitive index of fear responses and complementary to the classically used freezing measures to quantify fear-related and anxiety-related behaviors in mice.

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Poster

078. Emotion: Fear, Anxiety, and Pain II

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

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Topic: G.03. Emotion

Support: NIH R01 MH098348

NIH F99 NS105171

Ford Foundation Predoctoral Fellowship

Title: Negative life experiences contribute to racial differences in the neural response to threat

Authors: *N. G. HARNETT¹, M. D. WHEELLOCK¹, K. H. WOOD¹, A. M. GOODMAN¹, S. MRUG¹, M. ELLIOTT², M. SCHUSTER³, S. TORTOLERO EMERY⁴, D. C. KNIGHT¹

¹Psychology, Univ. of Alabama at Birmingham, Birmingham, AL; ²RAND Corporation, Santa Monica, CA; ³Boston Children's Hosp., Boston, MA; ⁴Univ. of Texas Hlth. Sci. Ctr., Houston, TX

Abstract: There are stark disparities in negative life experiences between African-American (AA) and European-American (EA) individuals. In aggregate, AA individuals are exposed to more violence, have greater rates of poverty, and experience more neighborhood disadvantage than EA individuals. These experiences may have deleterious effects on emotional function, and

contribute to racial disparities in mental health. Emotional function is mediated by neural circuitry that includes the prefrontal cortex (PFC), hippocampus, and amygdala. Therefore, disproportionate exposure to negative life experiences may impact neural activity within these regions. However, research in this area has been limited. Thus, the present study assessed brain function and behavior to determine the impact of negative life experiences on neural and behavioral function. AA and EA participants (n = 198) completed a Pavlovian fear conditioning procedure during functional magnetic resonance imaging (fMRI). Participants were recruited as part of a larger, longitudinal study that collected prospective measures of violence exposure, early life income, and neighborhood disadvantage. Participants' threat expectancies and skin conductance responses were continuously monitored. AA participants showed lower expectations of predictable threat than EA participants, but no group difference was observed during unpredictable threat. Further, AA participants demonstrated lower skin conductance responses to threat than EA participants. AA participants also showed reduced fMRI signal responses to threat than EA participants within the PFC, hippocampus, and amygdala. The brain and behavioral responses to threat also varied with individual differences in violence exposure, early life income, and neighborhood disadvantage. Importantly, group differences in the fMRI signal response were attenuated after accounting for negative life experiences. Our findings suggest that the developmental environment impacts the neural function that supports key emotional processes, and may partially underlie racial disparities in mental health.

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Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.01/CCC3

Topic: G.08. Drugs of Abuse and Addiction

Title: On the role of trait-anxiety in contributing to adolescent neuroplasticity in amphetamine-induced locomotor sensitization

Authors: C. A. CALHOUN¹, B. PLOTKIN², L. PINA¹, A. ALVES¹, *S. DONALDSON¹

¹Univ. of Massachusetts Boston, Boston, MA; ²Psychology, Umass Boston, Boston, MA

Abstract: Clinical populations present with anxiety disorders and often show risk-taking behaviors including drug use during adolescence, and often anxiety and substance use disorders are comorbid in adulthood. We hypothesize that the overlap between both disorders is modulated, in part, by neuroplasticity changes occurring within the mesocorticolimbic and stress adaptation pathways as a result of proinflammatory responses. The present study examined

differences in locomotor sensitization to amphetamine (AMPH) between high (HAn) and low (LAn) anxiety-like phenotyped adolescent male Long Evans rats. Anxiety profiles were screened using the elevated plus maze (EPM), and values on the EPM were operationalized as anxiety-like depending on the percent open arm entries (%OA Entry) and the percent time spent on the OA (%OA Time). We then employed a quartile analysis on the EPM (%OA Time and Entry) values. Values that fell within the highest quartile were categorized as LAn-like phenotypes, and those that fell within the lowest quartile were categorized as HAn-like phenotypes. HAn and LAn lines were exposed to either a moderate amphetamine (AMPH) sensitization or saline regimen: 4-day AMPH (4.0 mg/kg IP) or isotonic saline (SAL) every 48 h and measured for locomotor activity (LMA). After the 4th AMPH/SAL treatment and LMA testing, animals were given a 7-day extinction. Next, HAn and LAn lines were challenged with a low dose of AMPH (1.0 mg/kg IP) and later sacrificed. Results indicate that HAn adolescent rats showed greater distance traveled during habituation (pre-AMPH) and increasingly more activity over the 4-day AMPH treatment. Moreover, after a weeklong extinction, HAn animals also display the greatest sensitization response to the low-dose challenge (AMPH: 1.0 mg/kg IP). Compared to young and mature adult animals in our lab, the adolescents display greater sensitization over the consecutive treatment days, and during the challenge. We interpret these findings as evidence for augmented neuroplasticity important for reward-related learning and learning associations that may be unique for this developmental stage. Findings in the literature implicate the Toll-like receptor 4 (TLR4) in drug-induced neural sensitization and neuroplasticity, and thus, future work will elucidate differences in TLR4 mRNA and protein levels between HAn and LAn phenotypes exposed to repeated AMPH. Taken together, our work supports further use of this model for understanding novel pharmacotherapeutic targets in treating anxiety and drug addiction in adolescence

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Poster

079. Behavioral Studies of Amphetamines

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Topic: G.08. Drugs of Abuse and Addiction

Support: GACR 18-03806S

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Progres Q35 from Charles University

PharmaBrain CZ.02.1.01/0.0/0.0/16_025/0007444 funded from OP VVV

Title: ADHD symptoms and prenatal metamphetamine exposure

Authors: *A. OCHOZKOVA¹, L. MIHALCIKOVA², R. SLAMBEROVA³, A. YAMAMOTOVA⁴

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Abstract: ADHD is a mental disorder with a heterogeneous origin. The number of patients suffering from ADHD is growing. The pathophysiological mechanisms causing ADHD has not been clarified yet. There are few rat models of ADHD - genetic models, chemically induced models (ethanol, nicotine, PCBs, 6-hydroxydopamine lesion) or environmentally induced models (anoxia). Methamphetamine is the most commonly used drug in the Czech Republic that is often used by addicted pregnant women. MA may cause abnormalities in placenta and umbilical cord that result in hypoxia and malnutrition. The aim of the present study was to test prenatal MA exposure as a potential novel model of ADHD. The results will be compared with the results of the other models of the ADHD. Pregnant Wistar rats were divided into two groups. One group was daily administered with subcutaneous injection of MA (5 mg/kg), the other was injected with saline in the same volume. Male rat offspring were tested for their activity in a running wheel apparatus for 5 days on a 21st postnatal day, 35th postnatal day (in a nest - group of 8 pups) and then individually on 90th postnatal day. They were placed in the cage with free access to wheel, food and water for 5 consecutive days. Differences were detected between two experimental groups. Thus, our present data showing hyperactivity in MA offspring correspond with ADHD symptoms only partially. Other experiments have to be performed to test our hypothesis

Disclosures: A. Ochozkova: None. L. Mihalcikova: None. R. Slamberova: None. A. Yamamotova: None.

Poster

079. Behavioral Studies of Amphetamines

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Program #/Poster #: 079.03/CCC5

Topic: G.08. Drugs of Abuse and Addiction

Support: GAUK 560317

Progres Q35

260388/SVV/2018

PharmaBrain CZ.02.1.01/0.0/0.0/16_025/0007444

Title: Effect of paternal methamphetamine exposure on development of rat offspring

Authors: ***L. MIHALCÍKOVÁ**, A. OCHOZKOVÁ, R. ŠLAMBEROVÁ
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Abstract: Methamphetamine (MA) is one of the most commonly used drug in Czech Republic. Previous studies have proved the adverse effect of maternal drug abuse since the MA penetrates through placenta and secretes in the mother's breast milk. However, the contribution of father as a parent and half donor of genetic information is still unknown. Therefore, the present study analyzed the effect of paternal application (MA 5mg/kg) on behavioral development of rat offspring. The effect of paternal MA application on rat pup offspring has been investigated by behavioral tests (righting reflexes PD 1-12, negative geotaxis PD 9, rotating cylinder PD 23, and bar-holding test PD 23). While there were no significant differences in behavioral development of offspring induced by paternal MA application, there were sex differences in righting reflex and bar-holding tests on postnatal day 23. Males were more successful in righting reflexes whereas females achieved better results in bar-holding test. The other experiments did not show any significant difference in pup's development. Our results demonstrate that paternal drug abuse has negligible effect on rat pup development in comparison to the maternal drug exposure. However, the mechanisms of this impact have to be further investigated due to the fact that men's drug addiction and its influence on offspring is a current worldwide problem.

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Poster

079. Behavioral Studies of Amphetamines

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Topic: G.08. Drugs of Abuse and Addiction

Support: DGAPA-PAPIIT Grant IA205218
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DGAPA-PAPIIT Grant IN217918

Title: Maternal separation and social isolation: Factors that ease the development, extinction, and relapse of amphetamine-induced conditioned place preference in Wistar rats

Authors: ***L. MOLINA-ARCIA**¹, K. REYES-SANTIAGO¹, M. MENDEZ DIAZ², A. E. RUIZ-CONTRERAS³, O. PROSPERO-GARCIA⁴

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Abstract: Maternal separation (MS) and social isolation (SI) are important social variables to be considered when studying drug addiction. The aim of this study is to investigate the effect of MS and SI in the same subject on the development, extinction and relapse of amphetamine-induced Conditioned Place Preference (aCPP) on adult male and female Wistar rats. Rats were subjected to MS for 3h daily, from postnatal day (PND) 2 to PND 15; while control rats remained with the mother at all times (NMS). At PND 26, rats (NMS and MS rats) were randomly assigned into groups of 3 - 5 rats/cage (S) or were isolated (1rat/cage, SI). Subjects were divided into four groups: MS+SI, MS+ S, NMS+SI and NMS+ S. At PND 60, rats were exposed to amphetamine-induced CPP followed by 10 days of extinction and 1 day of relapse. Results indicate that male rats in all groups developed amphetamine-induced CPP. The MS+SI group did not extinguish this conditioning in comparison with the other groups that extinguished the CPP, hence, did not relapse. Regarding female rats, they, in all groups, showed amphetamine-induced CPP but none of them developed extinction. These results suggest that MS plus SI induce a robust aCPP. Moreover, female rats seem to be more vulnerable to develop aCPP.

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Poster

079. Behavioral Studies of Amphetamines

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Title: Different oxytocin responses to acute methamphetamine treatment in juvenile female rats perinatally exposed to stress and/or methamphetamine administration

Authors: ***A. HOLUBOVÁ**, S. PONIŠT, J. JURCOVICOVÁ, R. ŠLAMBEROVÁ
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Prague, Czech Republic

Abstract: Methamphetamine (MA) is an addictive psychostimulant, often abused by drug addicted women during pregnancy. The offspring of drug-addicted mothers are often exposed to perinatal stressors. The present study examines the effect of perinatal stressors and drug exposure

on plasma oxytocin (OXY) levels in female progeny. Forty-eight nulliparous adult female albino Wistar rats were divided into three groups according to drug treatment during pregnancy: intact controls (C); saline (SA, s.c., 1 ml/kg); MA (s.c., 5 mg/ml/kg). Litters were divided into four groups according to postnatal stressors: non-stressed controls (N); maternal separation (S); maternal cold-water stress (W); maternal separation plus cold-water stress (SW). On postnatal day 30, acute MA or SA (controls) injection was administered 1 hour prior to blood collection. The female offspring were sacrificed, and trunk blood was collected for OXY measurement using ELISA. Plasma OXY levels were significantly increased in prenatal controls after acute MA administration compared to acute saline controls. On the other hand, acute MA administration did not alter OXY levels in rats prenatally exposed to either SA or MA, indicating that long-term prenatal SA and/or MA exposure changes oxytocinergic system regulation in juvenile female rats. Repeated postnatal stress affected OXY release depending on prenatal treatment: In prenatally intact or MA treated rats, repeated stress exposure attenuate OXY release after acute SA or MA administration. In prenatally SA treated rats, no differences were observed in any of the postnatally stressed groups (S, W, SW) compared to non-stressed controls (N). As seen in this study, prenatal stress also plays an important role in endocrine development of affected offspring. Our data provide evidence that the regulation of OXY release is different for perinatal stress and MA administration.

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Poster

079. Behavioral Studies of Amphetamines

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Topic: G.08. Drugs of Abuse and Addiction

Support: Charles University project Progres Q35

GACR 18-03806S

OP VVV project PharmaBrain CZ.02.1.01/0.0/0.0/16_025/0007444

Title: The role of subcutaneous single injection in the effect of psychostimulant drugs and THC on the behavior of adult male rats

Authors: *R. SLAMBEROVA, K. NOHEJLOVA, A. OCHOZKOVA, L. MIHALCIKOVA
Dept. of Normal, Pathological and Clin. Physiol., Charles University, Third Fac. of Med., Praha, Czech Republic

Abstract: Psychostimulants as well as cannabinoids have been shown to affect a great variety of behaviors in both, humans and laboratory animals, in a serious manner. Our previous studies

repeatedly demonstrated that control groups with saline injection(s) have displayed changes in different behavioral tests when compared to absolute controls (without any injection). Therefore, our present study has set three aims: (1) to evaluate the effect of three different psychostimulant drugs; (2) to evaluate the effect of three doses of delta9-tetrahydrocannabinol (THC); and (3) to evaluate the effect of saline, ethanol solvent or injection per se (sham) on spontaneous behavior of adult male rats. LABORAS test (Metris B.V., Netherlands) was used to examine spontaneous locomotor activity and exploratory behavior in unknown environment during 1 hour. In Experiment 1, psychostimulant drugs were tested: single subcutaneous (s.c.) injection of amphetamine (5mg/kg), cocaine (5mg/kg) and MDMA (5mg/kg) was applied prior to testing. Control group received s.c. saline injection in the same volume (1 ml/kg). In Experiment 2, three doses of THC (1; 2 and 5 mg/kg, s.c.) were examined. As a control s.c. injection of solvent (ethanol) was used. In Experiment 3, injections of saline and ethanol were compared to group with sham s.c. injection and to group of absolute control without any injection. Our results demonstrated that (1) all psychostimulants increased the locomotion, distance traveled and the velocity, while decreasing the duration of immobility of adult male rats relative to saline controls. The most prominent effect was found after MDMA injection. (2) The effect of THC was dose dependent and was the most apparent within the first 10 minutes of the LABORAS test. (3) As a matter of the effect of injection: absolute controls (without injection) when compared to animals injected with ethanol, saline or sham displayed lowered time spent in immobility, traveled longer distance and displayed increased velocity. In conclusion, our data showed different changes in behavior of adult male rats after application of either psychostimulants or cannabinoids. Our findings also suggest that not only drugs, but also single injection per se affects behavior of laboratory animals in unknown environment. This effect seems to be associated with acute stress reaction.

Disclosures: **R. Slamberova:** None. **K. Nohejlova:** None. **A. Ochozkova:** None. **L. Mihalcikova:** None.

Poster

079. Behavioral Studies of Amphetamines

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Program #/Poster #: 079.07/CCC9

Topic: G.08. Drugs of Abuse and Addiction

Title: A machine learning approach using EEG data to detect methamphetamine craving induced in a virtual reality environment

Authors: ***X. DING**¹, **Y. LI**², **Y. QI**³, **Y. BI**³, **H. TANG**³, **D. LI**², **Z. PENG**²

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Abstract: The main aim of the present study was to use machine learning on EEG data to discriminate methamphetamine (METH) dependent individuals and normal controls in a virtual reality environment. One thousand and twenty-seven methamphetamine dependent individuals who were under compulsory rehabilitation (male, age range 18-51) and two hundreds and fifty-six healthy participants (male, age range 18-58) were recruited. The sample was matched regarding age and education background. Participants completed three VR sessions in a counterbalanced fashion. Each VR session presented METH-related cues. EEG data were collected throughout the three sessions by a low-cost, portable EEG system which recorded EEG on FP1, FP2, TP9 and TP10. Machine learning algorithm including random forests algorithm , logistic regression, adaboost algorithm were used to build classification model. The results showed that METH dependent individuals had different EEG pattern compared to normal controls under METH-VR session. Highest classification accuracy of 86% is obtained by adaboost algorithm, with 84% precision, 83% recall rate, and 83% f1 score. This study shows that the machine learning on EEG data can be a useful method for discriminating METH dependent individuals and normal controls. It indicates that this approach may be a valuable tool to help detect and evaluate METH craving.

Disclosures: **X. Ding:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Adai Technology Co., Ltd. **Y. Li:** A. Employment/Salary (full or part-time);; Adai Technology Co., Ltd.. **Y. Qi:** None. **Y. Bi:** None. **H. Tang:** None. **D. Li:** A. Employment/Salary (full or part-time);; Adai Technology Co., Ltd. **Z. Peng:** A. Employment/Salary (full or part-time);; Adai Technology Co., Ltd..

Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.08/CCC10

Topic: G.08. Drugs of Abuse and Addiction

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Title: Methamphetamine self-administration in female Long Evans rats

Authors: ***A. DAIWILE**, S. JAYANTHI, R. PATEL, M. T. MCCOY, B. LADENHEIM, J. L. CADET
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Abstract: Methamphetamine (METH) is an extremely addictive drug and is one of the most abused illegal drug in world. METH addicts exhibit a variety of cognitive and behavioral deficits such as impaired attention, memory, processing speed to decision-making. Numerous studies

have investigated the behavioral and biochemical effects of METH in male rats, but few groups have conducted similar studies in female rats. Herein, we have used female Long Evans rats and trained them to self-administer METH (0.1 mg/kg/infusion, IV) on an FR-1 schedule for 20 days using a pattern of two 3-h sessions/day separated by 30 min breaks. After completion of SA training, they underwent two tests of cue-induced drug seeking under extinction conditions on withdrawal day 2 (WD2) and 30 (WD30). Thus, during the two tests, active lever responses did not result in any METH infusion. Female rats escalated the number of METH infusions over time and obtained an average of 7.8 mg/kg of total METH intake. Inspection of the behavioral data revealed that among the METH SA rats, there were two phenotypes of relatively low METH takers (n=4) and high METH takers (n=12). In addition, some (n = 8) of the high METH takers showed obvious escalation of METH self-administration (SA) whereas others (n=4) started with a high number of METH infusions that plateaued at the high levels. No differences were observed in the average body weight between the groups during METH SA training. These results showed that female rats take METH according to different patterns of drug infusion. Potential differences in biochemical and molecular consequences of these different patterns of METH infusions are presently being investigated.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: JSPS KAKENHI Grant JP15K04180
JSPS KAKENHI Grant JP16K04419

Title: Enhanced methamphetamine-induced conditioned place preference in risk-taking rats

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Abstract: Patients with psychiatric disorders, such as gambling disorder and substance use disorder, tend to exhibit maladaptive decision making. Previous studies have shown that patients depending on drugs and gambling are likely to exhibit risk-taking behaviors. In the present study, we assessed individual differences in risk-taking behavior using a rat version of the Iowa gambling task (rGT), and investigated the relationship between risk-taking behaviors and

vulnerability to drug dependence using methamphetamine (MAP)-induced conditioned place preference (CPP). In the rGT using a radial arm maze, male Long-Evans rats (7-8 weeks old at the beginning) were trained to choose one of three choice arms (a low-risk/ low reward (L-L) arm, a high-risk/ high reward (H-H) arm and an empty arm) in 16 trials per day for 14 days. While choice of the L-L arm resulted in frequent (87.5%) small rewards (a 45 mg pellet) with infrequent (12.5%) negative outcomes (a quinine-coated pellet), choice of the H-H arm resulted in infrequent (12.5%) large rewards (six pellets) with frequent (87.5%) negative outcomes. We assigned the rats to two groups: the risk-taking and optimal choice groups on the basis of the percentage of choice for the H-H arm after the 9th day. The rats that scored in the higher 25% of the distribution were regarded as the risk-taking group (n=7) while those in the lower 25% of the distribution were regarded as the optimal choice group (n=7). MAP-induced CPP consisted of 7 sessions, including habituation, baseline assessment, conditioning, a preference test, extinction, an extinction test and a reinstatement test. Conditioning sessions were conducted for 6 consecutive days, and rats received a pairing of either MAP (0.5 mg/kg, i.p.) or saline with a specific compartment once a day, and the pairing was alternately carried out 3 times each. During the extinction sessions, rats were confined to the MAP-paired compartment for 30 min once a day without any drug injection. Rats were treated with a lower dose of MAP (0.1 mg/kg, i.p.) immediately before the reinstatement test. In all three tests, rats were allowed to explore the chamber for 15 min, and the time spent in each compartment was recorded. The results demonstrated a significant positive correlation between the percentage of choice for the H-H arm and the preference score for the MAP-paired compartment in the preference test, but not in the extinction and reinstatement tests. These findings suggest that risk-taking rats are more likely to be more vulnerable to drug dependence.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: MARC GM-08807
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LSAMP HRD-1302873

Title: Impact of environmental familiarity on the rewarding response to methamphetamine

Authors: *B. C. CORTES¹, K. A. TRUJILLO²

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Abstract: Methamphetamine is a powerful psychomotor stimulant that is widely abused due to its rewarding and addicting properties. Though there is much research on the effects of methamphetamine, few studies have assessed the influence of environmental familiarity on the rewarding effects of the drug. The present study examined ultrasonic vocalizations (USVs) and locomotor activity in response to methamphetamine (METH 0.3 mg/kg or 2.0 mg/kg) in Sprague-Dawley rats. USVs are indicative of affective states, with 50 kHz USVs reflective of positive affect and reward. Locomotor activity assesses the stimulant response to the drug, which is thought to be an indirect reflection of drug reward. Familiarity was established by multiple exposures to the testing environment coupled with a saline injection (familiar group). A second group received saline injections in home cages and had no previous exposure to the testing environment (unfamiliar group). It was hypothesized that USVs would be greater in the familiar group than the unfamiliar group, but that the locomotor stimulant effect would not differ between groups. As hypothesized, the group familiar with the testing environment produced a greater number of 50 kHz USVs than the unfamiliar group in response to methamphetamine. The familiar group also showed a greater locomotor stimulant response to methamphetamine during the early portion of the timecourse. These results suggest that the expression of USVs is suppressed in a novel environment and that repeated exposure to the experimental apparatus may aid in unmasking the rewarding properties of methamphetamine. A better understanding of the impact of the environment on the expression of reward will enable more accurate models of addiction.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA042211

Title: Self-administration of entactogen psychostimulants under extended access conditions in female rats

Authors: *J. D. NGUYEN, S. VANDEWATER, Y. GRANT, S. KHOM, M. ROBERTO, M. A. TAFFE

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Abstract: Entactogen psychostimulants such as 3,4-methylenedioxymethcathinone (methylone), 3,4-methylenedioxypentadron (pentylone), and 3,4-methylenedioxymethamphetamine (MDMA) are commonly abused substances; however, there are relatively limited data available

that elucidate the abuse liability of these drugs. The goal of this study was to determine if intravenous self-administration of methylone or pentylone under extended access conditions results in escalation of intake in female rats, similarly to the escalation previously reported for male rats trained to self-administer methylone, mephedrone or MDMA. It was hypothesized that extended access sessions would lead to escalated self-administration of methylone and pentylone, compared to MDMA. Groups of female Wistar rats were trained to self-administer methylone, pentylone, MDMA (all at 0.5 mg/kg/infusion) or saline vehicle using a fixed-ratio 1 (FR1) response contingency in 6 hour sessions. Progressive Ratio (PR) dose-response testing was completed using the respective training drug (0.125-2.5 mg/kg/infusion). Rats trained on methylone and pentylone increased their intake to an approximately similar extent and received higher number of infusions compared to rats trained on MDMA. Pentylone-trained rats reached higher breakpoints than methylone and MDMA-trained groups in PR tests. These data confirm that female rats readily acquire the self-administration of methylone, pentylone, and MDMA under 6 hour extended access conditions and suggest the increased abuse liability of methylone and pentylone relative to MDMA.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: This research was supported financially by Student-Faculty Research funds provided by Dickinson College

Title: Increasing number of CS extinction trials blocks context-specific sensitization in mice

Authors: *A. S. RAUHUT¹, A. L. STASIOR²

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Abstract: Associative learning processes have been proposed to contribute to behavioral sensitization; however, previous research has shown that extinction does not alter expression of behavioral sensitization in rodents. The number of conditioned stimulus (CS) exposures has been shown to be an important variable in determining the rate and robustness of extinction in the Pavlovian conditioning literature. Thus, the present experiment examined the effect of varying the number of CS exposures on the rate of extinction of conditioned hyperactivity and the subsequent expression of context-specific sensitization in mice. The experiment consisted on 3

phases: acquisition, extinction and tests for context-specific sensitization. During acquisition, male, Swiss Webster mice (n = 10/group) received an injection (subcutaneous, s.c.) of methamphetamine (0.5 mg/kg) immediately before (paired) or after (unpaired) five, 30-minute locomotor activity sessions. Following the acquisition phase, the extinction phase began and lasted 10 days. At this time, paired and unpaired mice received an injection of vehicle and placed in the locomotor activity chambers for either 5 (1 session/day x 5 days, once in the morning) or 20 (2 sessions/day x 10 days, once in the morning and once in the afternoon approximately 4 hours apart) sessions. The 5 extinction sessions occurred on the last 5 days of the 10-day extinction phase so that the 5- and 20-extinction session mice were tested for context-specific sensitization following their respective extinction treatments. Two control groups (Paired-Rest and Unpaired- Rest) were included that did not undergo extinction and remained in their home cages for the entirety of this phase. The test for context-specific sensitization occurred 24 hours after the last extinction session. All mice received an escalating methamphetamine-injection regimen (0.25 --> 0.5 --> 1.0 mg/kg, 1 dose/day) and tested for a 60-minute period in the locomotor activity chambers. It was found that Paired-Rest mice showed greater locomotor activity compared to their Unpaired-Rest counterparts following the low methamphetamine-challenge dose (i.e., context-specific sensitization). However, Paired mice that received 20, but not 5, extinction sessions failed to show context-specific sensitization. These results add further support for the role of associate learning processes in context-specific sensitization and suggest that factors (e.g., number of CS extinction trials) that promote extinction may alter the expression of context-specific sensitization.

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Poster

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Program #/Poster #: 079.13/DDD1

Topic: G.08. Drugs of Abuse and Addiction

Title: Neuroinflammation and amphetamine sensitization in the adolescent Long Evans rat

Authors: *B. PLOTKIN¹, C. A. CALHOUN², T. DONALDSON⁴, L. PINA³, A. ALVES³

¹Psychology, Umass Boston, Boston, MA; ²Psychology, Univ. of Massachusetts Boston, Somerville, MA; ³Univ. of Massachusetts Boston, Boston, MA; ⁴Psychology, Univ. of Massachusetts, Boston, MA

Abstract: Repeated exposure to drugs of abuse activates the immune system and the induction of the immune system alters the subsequent response to drugs of abuse (Snider et al., 2012). Exposure to the endotoxin and immune activator, lipopolysaccharide (LPS), *in utero* and in neonates leads to the up-regulation of striatal dopamine receptors, and increases the behavioral

response to amphetamine. The implications of immune activation on reward-related striatal systems and/or amphetamine behaviors have yet to be investigated during adolescence, a particularly vulnerable time of increased risk-taking and novelty seeking behaviors such as drug use (Wills, Vaccaro, & McNamara, 1994). In this experiment, we investigated the impact of a single LPS (0.1 mg/kg IP) (N=15) injection in adolescent Long Evans male rats 1 h prior to the first amphetamine treatment (4 mg/kg, IP); animals received amphetamine or saline for a total of 4 days at 48 h intervals and locomotor activity (LMA) was recorded. A one-week extinction period was followed by a low dose challenge (1.0 mg/kg AMPH IP). Animals were sacrificed on the final day of testing and brains were flash frozen and stored at -80° C for immunohistochemistry. Results indicate a single LPS injection decreased weight gain, and significantly lowered the Day 1 response to AMPH. Interestingly, across the 4-day AMPH treatment, prior exposure to LPS significantly increased locomotor response. Moreover, the single LPS treatment markedly enhanced the sensitized response to a low challenge dose (1.0 mg/kg IP) of AMPH following the 7-day extinction period. The LPS-induced AMPH differences in the LMA were apparent for distance traveled, rears, and stereotypies. Taken together, our findings reveal that exposure to the endotoxin, LPS, in adolescent rats increases AMPH locomotor sensitization. This interaction of neuroimmune activation and repeated AMPH at this developmental stage offers novel insight into mechanisms that may impact later life vulnerability to drugs of abuse.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NRF 2017R1E1A2A01079599
K18181

Title: Mediation of central amygdala in acupuncture inhibition of methamphetamine-induced behavior in rats

Authors: ***H.-Y. KIM**, M. S. KIM, E. Y. JANG, D. H. KIM, K. M. SONG, Y. FAN, J. H. SHIN
Daegu Haany Univ., Daegu, Korea, Republic of

Abstract: Abstract

Methamphetamine(METH) activates mesolimbic dopaminergic system and generates the reinforcing effects. Our previous studies showed that acupuncture attenuates drug-seeking

behaviors by enhancing GABAergic transmission ventral tegmental area and reducing mesolimbic dopamine release in the nucleus accumbens (NAc). The effects of acupuncture on METH-induced behaviors and the neural pathways mediating the effects are unclear. We investigated whether acupuncture attenuates locomotor activity by acute administration of METH and the effects are mediated through central amygdala (CeA). Locomotor activity was measured with a video tracking system that provided automatic measures of traveled distance. Ultrasonic vocalizations (USVs) were recorded in customized sound-attenuating chambers that consisted of two boxes to minimize exterior noise. Acupuncture needles were inserted into either HT7 (located on the transverse crease of the wrist of the forepaw, radial to the tendon of flexor carpi ulnaris muscle) or SI5 (located on the ulnar end of the transverse wrist crease) and stimulated by using mechanical acupuncture instrument that was designed to vibrate needles mechanically. Acute injection of METH (0.5mg/kg, i.p) significantly increased locomotor activity, compared with the values of pretreatment, which lasted up to about 30 min with a peak at 10 min. Mechanical stimulation of needles inserted into HT7 or SI5 inhibited the increase of locomotion produced by METH and 50-kHz USVs. The acupuncture effects were prevented by electrolytic lesion of CeA. These results suggest that acupuncture suppresses METH-induced affective states and locomotor behavior and such effects were mediated via CeA.

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Poster

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K18181 to HYK

Title: Effect of acupuncture on methamphetamine-seeking behavior in rat mediation of group II mGluR

Authors: *E. JANG¹, K. SONG¹, M. KIM¹, H. JANG², S. CHANG¹, C. YANG¹, H. KIM¹
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Abstract: Methamphetamine (METH) mediates the reinforcing effect via activation of the mesolimbic dopamine system in the brain. We have previously demonstrated that acupuncture reduces locomotor activity, ultrasonic vocalizations, extracellular dopamine release in the

nucleus accumbens (NAc), and brain temperature (an indicator of local brain metabolic activity) in acute methamphetamine-treated rats and suppresses cocaine- and alcohol-seeking behaviors. In addition, acupuncture inhibition of METH-induced NAc temperature was prevented by pre-treatment with a group II metabotropic glutamate receptors (mGluR2/3) antagonist EGLU into the NAc or mimicked by injection of an mGluR2/3 agonist DCG-IV into the NAc. This study was conducted to investigate the effect of acupuncture on drug priming-induced reinstatement of METH-seeking behavior and its mediation of mGluR2/3 in the NAc. Male Sprague-Dawley rats were trained to self-administer METH (0.05 mg/kg/infusion) for 2-3 weeks (2 hours/day) followed by extinction and then drug priming (METH, 0.5 mg/kg, i.p.). Acupuncture was applied at bilateral Shenmen (HT7) points for 1 min immediately after injection of METH. mGluR2/3 antagonist was infused into the NAc prior to METH injection. Priming injection of METH reinstated drug-seeking behavior in the rats self-administering METH, which was prevented by acupuncture at HT7. And, such acupuncture effects were abolished by pre-treatment with a mGluR2/3 antagonist EGLU into the NAc or mimicked by injection of an mGluR2/3 agonist DCG-IV into the NAc. These results suggest that acupuncture reduces METH-seeking behavior through mediation of accumbal mGluR2/3.

Key word: acupuncture, methamphetamine, self-administration, mGluR2/3, nucleus accumbens
Supported by: NRF 2016R1D1A1B03935206 to EYJ and NRF 2017R1E1A2A01079599, K18181 to HYK.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: DA024705

Title: Examination of a methamphetamine vaccine: Behavioral response in male rats

Authors: *M. JAVADI PAYDAR¹, M. E. OLSON², S. A. VANDEWATER¹, K. D. JANDA², M. A. TAFFE¹

¹Dept. of Neurosci., The Scripps Res. Inst., La Jolla, CA; ²Dept. of Chemistry, Dept. of Immunol. and Microbial Sci., The Skaggs Inst., La Jolla, CA

Abstract: BACKGROUND: Active immunization of rats with vaccines programed to elicit an immune response against methamphetamine (METH) have been shown to produce drug-specific antibodies, which in turn attenuate the psychoactive and locomotor effects of METH. Here, we

describe whether active vaccination against METH could alter intravenous METH self-administration in rats. **METHODS:** Male Wistar rats (N=36) were vaccinated with tetanus toxoid (TT), MH6-TT or sGly-TT conjugate vaccines. Effects of vaccination on the acquisition of METH self-administration and wheel activity were determined. METH self-administration was initially determined under three training dose conditions (0.05, 0.1, then 0.025 mg/kg/inf), during post-acquisition dose-substitution (0, 0.01, 0.05, 0.10, 0.50 mg/kg/inf) and finally as a 0.0125 mg/kg/inf maintenance condition. Plasma METH concentrations were determined 30 minutes after an acute challenge dose of 3.2 mg/kg METH. **RESULTS:** Effective antibody levels were only produced in MH6-TT-vaccinated rats and METH self-administration was altered in the MH6-TT group when 0.0125 mg/kg/inf was available as the maintenance dose. **CONCLUSIONS:** These data demonstrate that immunopharmacotherapy provides functional protection against physiological and behavioral disruptions induced by METH.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: Regis University FRSG
Regis University SRSG

Title: The effect of exercise on the cognitive consequences of methamphetamine abuse

Authors: *H. R. JENKINS, T. B. VU, B. R. FINE, A. N. FRICKS-GLEASON
Regis Univ., Denver, CO

Abstract: Methamphetamine (METH) is a widely used psychostimulant drug, and its use in the United States has reached a near-epidemic in the past 15 years, due to the ease with which METH can be manufactured, as well its highly addictive properties. METH use costs the government billions per year through crime, foster care, lost workplace productivity, and other social problems, in addition to causing destructive effects in the lives of users. In humans, METH abuse has been shown to result in long-lasting brain injury as well as significant cognitive impairments. METH interacts with the catecholamine nerve terminals in the brain, inducing non-exocytotic transmitter release, which results in the initial euphoria after taking the drug but then leads to long-lasting brain injury for the user. The neurotoxic effects of the drug are responsible for inducing the cognitive consequences associated with abuse, which include impairments in memory, attention, executive functioning, and decision making skills. The

memory impairments caused by METH are seen as the most prominent and persistent cognitive problems, because they interfere with the abuser's ability to adhere to and benefit from addiction treatment. Therefore, it is of utmost importance to find ways to attenuate these cognitive deficits and thereby improve treatment outcomes for METH users. Exercise is well known for its beneficial physiological effects, and its cognitive enhancing properties. In terms of METH abuse, previous research has demonstrated that in an animal model, post-METH voluntary running can significantly attenuate the dopaminergic neurotoxicity induced by a binge regimen of the drug, potentially due to the upregulation of neuronal growth factors through exercise. Therefore, we have reason to suspect that exercise may also ameliorate the cognitive deficits induced by METH. The present study examined the effects of post-METH exercise on two well-validated tests of memory in an animal model: object recognition and odor recognition, in hopes of demonstrating an attenuation of METH-induced memory specific cognitive impairments as a result of exercise.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Ketamine, but not MK-801, reduces methamphetamine-induced locomotor activity: Implications for treatment of addiction

Authors: C. CHAVEZ¹, A. ROCHA¹, *K. A. TRUJILLO²

²Dept. of Psychology, ¹California State Univ. San Marcos, San Marcos, CA

Abstract: Methamphetamine (METH) is a potent and addictive psychomotor stimulant. Previous work from our laboratory has demonstrated that a low dose of ketamine (KET) inhibits the locomotor stimulant effect of METH when administered concurrently with, or 15-minutes prior to, METH. Although the overt behavioral effects of KET are short-lived, some effects are longer-lasting, most notably the antidepressant effects of the drug. The present study examined the ability of KET to affect the stimulant response to METH when administered 1-hour prior to METH. Since NMDA receptors are thought to play a role in the behavioral response to KET, we also examined the effect of dizocilpine (MK-801), a potent and selective NMDA receptor antagonist. Adult Sprague-Dawley rats received KET (10 mg/kg s.c.) or MK-801 (0.1 mg/kg

s.c.) followed 1-hour later by METH (1.0 mg/kg s.c.). Locomotor activity was assessed for 150 minutes following the first injection. It was hypothesized that KET or MK-801 1-hour prior to METH would decrease the stimulant response to the drug. KET alone exhibited an increase in horizontal activity immediately after injection compared to saline control groups, this effect lasted 5-10 minutes. MK-801 produced a more potent stimulant effect that lasted approximately 2 hours. Consistent with our hypothesis, KET reduced METH-induced locomotor activity. Specifically, KET reduced METH-induced horizontal activity and abolished METH-induced rearing behavior. However, in contrast to our hypothesis, MK-801 did not decrease METH-induced locomotor activity, rather it promoted horizontal activity; although MK-801 did abolish METH-induced rearing behavior. These results demonstrate that KET reduces the stimulant effects of METH and that the effect is likely not due to NMDA receptor blockade. To the extent that locomotor stimulation reflects rewarding effects of METH, the results suggest that KET may interfere with METH reward. These results are consistent with suggestions that ketamine may be useful in the treatment of addiction.

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Support: AA006420

AA013498

AA015566

AA013517

AA020893

FWF J-3942

Title: Intravenous self-administration of MDMA and pentylone dysregulates GABA and KOR-signaling the central nucleus of the amygdala of female Wistar rats

Authors: *S. KHOM, J. D. NGUYEN, S. VANDEWATER, Y. GRANT, M. A. TAFFE, M. ROBERTO

Dept. of Neurosci., The Scripps Res. Inst., La Jolla, CA

Abstract: Dynorphin/kappa-opioid receptor (KOR) signaling plays a critical role in multiple physiological processes including learning and memory, emotional control, stress response and pain as well as in pathological conditions such as addictive disorders, epilepsy, depression, schizophrenia, and chronic pain (Schwarzer, 2009). Both acute and chronic MDMA

administration have been shown to affect dynorphin levels in several brain regions (Johnson et al., 1991; Di Benedetto et al., 2006); however there have been no functional studies on cellular effects of MDMA or structurally similar entactogen psychostimulants in the central amygdala (CeA). We examined the effects of the KOR agonist U-50488 and the KOR-antagonist nor-binaltorphimine (norBNI) on spontaneous, action-potential independent GABAergic neurotransmission (miniature postsynaptic inhibitory currents, mIPSCs) in the CeA (medial subdivision) of female Wistar rats trained to intravenously self-administer MDMA, pentylone and saline-vehicle (following 18 hours abstinence). MDMA self-administration significantly increased amplitudes and decay times of mIPSCs compared to saline-controls and pentylone-trained rats suggesting that MDMA self-administration causes a profound change in postsynaptic GABA_A receptor function, while basal GABA transmission in the CeA of pentylone-trained animals did not significantly differ from saline-controls. In addition, mIPSC frequency (indicating increased presynaptic GABA release) was significantly increased in rats trained to self-administer MDMA compared to pentylone, suggesting different presynaptic neuroadaptive processes. In saline-controls, application of the KOR agonist U50488 significantly decreased mIPSC frequency (63±4% of control), while the KOR-antagonist norBNI significantly increased mIPSC frequency (119±8% of control) indicating a tonic regulation of GABAergic transmission by endogenous dynorphin in the CeA. Interestingly, both MDMA or pentylone self-administration caused a profound disruption of the dynorphin/KOR system: while KOR activation using U-50488 significantly decreased mIPSC frequency in both groups similar to saline-controls indicative of the presence of functional KORs, no effect of norBNI on mIPSC frequency was observed in either group, suggesting a loss of tonic dynorphin signaling. Thus, our data suggest that self-administration of MDMA and pentylone induces neuroadaptive changes in spontaneous GABA transmission and disrupts KOR-signaling in the CeA, a brain region critically involved in addictive processes.

Disclosures: J.D. Nguyen: None. S. Vandewater: None. Y. Grant: None. M.A. Taffe: None. M. Roberto: None.

Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.20/DDD8

Topic: G.08. Drugs of Abuse and Addiction

Support: BX003304

DA034140

AA020098

Title: Inhibition of D1R expressing neurons in the dorsal striatum promotes meth addiction-like behavior

Authors: ***R. J. OLIVER, JR**, K. KHARIDIA, 92161, M. FANNON, C. MANDYAM, 92121 Anesthesiol., VA San Diego, San Diego, CA

Abstract: Evidence from previous studies indicates that methamphetamine (Meth) self-administration upregulates dopamine D1 receptors (D1Rs) in the dorsal striatum. It is therefore hypothesized that D1 receptor expressing medium-sized spiny neurons in the dorsal striatum may contribute to reinforcing effects of Meth and produce dependence-like behavior. Here we seek to determine if inhibiting D1R expressing neurons in the dorsal striatum alters Meth self-administration. A viral vector-mediated approach was used to overexpress the inhibitory (G_i coupled-hM4Di) designer receptors exclusively activated by designer drugs (DREADDs) engineered to only respond to exogenous ligand clozapine-N-oxide (CNO). Preliminary findings from behavior data reveal that CNO treatment in animals overexpressing DREADDs increased responding for Meth compared to vehicle saline in a within subject treatment paradigm. CNO treatment in animals that did not express DREADDs did not alter responding for Meth, demonstrating specificity for DREADD-CNO interaction. Postmortem tissue analysis reveal that CNO treatment reduced neuronal activation in the dorsal striatum compared to non DREADD controls and animals that self-administered saline. Ongoing studies will determine the cellular mechanisms underlying reduced neuronal activation in the dorsal striatum in DREADD-CNO injected rats. Our studies indicate that normal functioning and activity of D1R expressing neurons in the dorsal striatum is necessary for reducing Meth addiction-like behavior.

Disclosures: **R.J. Oliver:** None. **K. Kharidia:** None. **M. Fannon:** None. **C. Mandyam:** None.

Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.21/DDD9

Topic: G.08. Drugs of Abuse and Addiction

Support: Zardi Gori Foundation, 2018

Title: 5-HT_{2A/C} subtype and arginine-vasopressin V_{1a} receptors modulate rewarding, prosocial and anxiolytic effects induced by two synthetic phenethylamines in zebrafish

Authors: ***L. PONZONI**¹, D. BRAIDA², M. SALA¹

¹Inst. of Neurosci., CNR, Milano, Italy; ²Dept. of Med. Biotech. and Translational Med., Univ. degli Studi di Milano, Milano, Italy

Abstract: DOB and PMA are two phenethylamines sold openly through websites and associated with psychostimulant activity and toxicity (1,2). Both drugs and the classical phenethylamine 3,4-methylenedioxymethamphetamine (MDMA) have been found to interact with serotonin receptors in rodents (3). There is growing evidence that the neuropeptide oxytocin (OT) can modulate drug-related reward and may act as a pharmacological treatment of drug dependence. Aquatic models such as zebrafish have been recognized as useful models to test the toxicity of addictive drugs and to evaluate their potential clinical applications (4).

The aim of our work was to investigate the role of serotonin 5-HT_{2A/C} like- and of arginine-vasopressin V_{1a} receptors on reward, social preference and anxiety-like behaviour induced by DOB and PMA, compared to MDMA, using ritanserin and SR49059, two antagonists of serotonin 5HT_{2A/C} and the arginine-vasopressin V_{1a} subtype receptor, respectively.

MDMA and its derivatives dose-dependently induced rewarding, anxiolytic effect and an increase in social preference following a biphasic trend, being PMA the most potent. Both ritanserin and SR49059 significantly blocked all the effects, suggesting the involvement of serotonin 5-HT_{2A/C} and arginine-vasopressin- like receptors. The current study demonstrated a rewarding, prosocial and anxiolytic effect of DOB and PMA in zebrafish and focused on the mechanisms of their action suggesting a potential clinical application in drug dependence.

1. Liechti, (2015) Swiss Med Wkly. 145:w14043
2. Jang et al. (2016) Forensic Sci Int. 266:e27-31
3. Owens et al (2015) Swiss Med Weekly. 145,w14043
4. Kyzar, Kalueff (2016) Zebrafish 10.1089/zeb.2016.1251

ACKNOWLEDGEMENTS

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Disclosures: L. Ponzoni: None. D. Braida: None. M. Sala: None.

Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.22/DDD10

Topic: G.08. Drugs of Abuse and Addiction

Support: Research grant 1-438-5836 from Deanship of Graduate Studies and Scientific Research, Taif University, SA.

Title: Role of venlafaxine in relapse to methamphetamine seeking: Potential treatment option for drug dependence

Authors: *Y. ALTHOBAITI¹, A. H. ALMALKI²

¹Pharmacol. and Toxicology, ²Pharmaceut. and Medicinal Chem., Taif Univ., Taif, Saudi Arabia

Abstract: Drug addiction is a critical health issue in Saudi Arabia and worldwide. Of note, amphetamine is the most commonly used psychostimulant. According to the world drug report, Saudi Arabia reported the highest amphetamine-type stimulant seizure (11 tons) in 2011 and methamphetamine (METH) is the most commonly abused stimulant worldwide. Importantly, relapse to drug use is the most critical challenge in treating the addictive disorder. Several recent studies showed that glutamate release in the brain during re-exposure to different stimuli, such as re-exposure to the drug after a period of abstinence, is the primary neurochemical reason of relapse to drug use. Thus, preventing glutamate release is an important strategy in the management of relapse to drug use. Venlafaxine (VEN), well-known antidepressant, showed efficacy in blocking evoked glutamate release in the brain and there is no study investigated its role in relapse to METH seeking. In this study, we investigated the effects of VEN on relapse to METH seeking in a rat model of drug addiction using conditioned place preference (CPP). The CPP apparatus consists of two conditioning chambers which are distinguished by both visual and tactile cues. The CPP experiment consists of four distinct phases; the preconditioning, conditioning, extinction, and reinstatement phase. Rats were allowed to explore the entire CPP apparatus without any treatment during the preconditioning phase. Each group then received either saline or METH (1 mg/kg, i.p.) for eight days during the conditioning phase, followed by 21 days treatment with either saline or VEN (10 mg/kg, i.p.) during the extinction phase. Finally, rats were tested for reinstatement produced by an i.p. injection of METH (1 mg/kg). METH treatment during the conditioning phase has significantly increased time spent in the METH-paired chamber as compared to the saline-paired chamber. No significant changes in time spent in either saline- or METH-paired chambers following the extinction phase. A priming dose of METH significantly increased time spent in the METH-paired chamber as compared to the saline-paired chamber in animals that were treated with saline during the extinction phase. Interestingly, VEN treatment blocked the reinstatement effect of METH. These promising findings might open the path for further testing of the beneficial effects of VEN in drug dependence.

Disclosures: Y. Althobaiti: None. A.H. Almalki: None.

Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.23/DDD11

Topic: G.08. Drugs of Abuse and Addiction

Title: Role of orexinergic system in methamphetamine-induced drug addiction

Authors: *C. LEE¹, G. PARK², J.-H. JANG¹

¹Sch. of Medicine, Keimyung Univ., Daegu, Korea, Republic of; ²Col. of Pharm., Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: Methamphetamine (METH) is a powerful neurotoxic psychostimulant characterized to affects activity of dopamine transporters leading to blockage of dopamine (DA) uptake into the synaptic vesicle as well as DA reuptake through the plasma membrane inducing synaptic DA release, which resulted in continuous excess extracellular DA levels in the synaptic cleft. Orexinergic system has been reported to play crucial roles in regulation of arousal, wakefulness, and motivated behaviors for drug abuse. In this study, we have investigated the role of orexin and/or orexin receptors on METH-induced addictive behaviors by conducting conditioned place preference (CPP) test using SB334867, an orexin-1 receptor antagonist. The changes in the dopaminergic system integrity and orexin-related signaling molecules were examined to elucidate underlying molecular mechanisms. C57BL/6 mice were administered with METH (1 mg/kg, i.p.) alternately on each other day for 8 days, allowed to undergo withdrawal period without injection of METH for additional 8 days, and then challenged again with METH. METH-administered mice exhibited increased levels of orexin and orexin-1 receptor in the brain regions of hippocampus, striatum, hypothalamus, and amygdala. The application of SB334867 significantly attenuated the acquisition, expression, and reinstatement of the METH-induced CPP. These findings suggest that orexinergic system may play a role in the acquisition and relapse of METH-induced addictive behaviors, thereby providing a novel therapeutic target for the METH addiction.

Disclosures: C. Lee: None. G. Park: None. J. Jang: None.

Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.24/DDD12

Topic: G.08. Drugs of Abuse and Addiction

Title: The effects of a TSPO agonist (Ro5-4864) on cocaine and methamphetamine drug-primed and cue-reactivity in rats

Authors: *G. F. GUERIN¹, C. M. KELLER¹, S. M. HAROLD¹, A. MEAUX¹, L. HERNDON¹, K. BJORNSON², G. LI³, J. M. COOK³, N. E. GOEDERS¹

¹LSUHSC-S, Shreveport, LA; ²Hobart and William Smith Colleges, Geneva, NY; ³Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Research has shown that stress and the activation of the HPA axis play a major role in reward and drug reinforcement. Benzodiazepines, such as alprazolam and oxazepam, interact

with $\alpha 1$ subunits of GABA_A receptors to increase dopaminergic activity in the VTA. However, oxazepam also has an affinity for a second binding site, the translocator protein 18 kDa (TSPO), also known as the peripheral benzodiazepine receptor. Binding at TSPO increases neurosteroid levels, which can reduce dopamine levels in regions associated with reward. Previous research has shown that oxazepam reduces cocaine self-administration as well as two measures of cocaine craving (i.e., cue reactivity and reinstatement) in rats. Another experiment showed that Ro5-4864, a benzodiazepine derivative of diazepam with selective affinity for TSPO, dose dependently decreased methamphetamine self-administration in male and female rats without affecting food self-administration. The current study tested the effects of selective TSPO binding on cocaine and methamphetamine drug-primed reactivity and cue-reactivity. Male and female Wistar rats were trained to self-administer cocaine or methamphetamine. After stabilization of responding and a two-week abstinence period, rats were pretreated with Ro5-4864 or vehicle before testing in either a drug-primed reactivity or cue-reactivity session that measured drug-seeking behavior. The rats were once again trained to self-administer cocaine or methamphetamine, placed into abstinence, and pretreated with vehicle or Ro5-4864 before reactivity testing. Drug-primed responding with cocaine and methamphetamine was reduced by Ro5-4864 in both male and female rats. However, cue-reactivity was reduced only in rats trained with methamphetamine. These data suggest that selective binding to TSPO may be a potential treatment for methamphetamine relapse. This research also demonstrates the potential for the development of other TSPO variants for use in future experiments.

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Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 079.25/DDD13

Topic: G.08. Drugs of Abuse and Addiction

Support: USPHS Grant DA042211

Title: Evaluation of the potency and reinforcing efficacy of ring-substituted synthetic cathinones in rats

Authors: ***E. HARVEY**¹, **K. CREEHAN**¹, **M. JAVADI-PAYDAR**¹, **J. NGUYEN**¹, **S. VANDEWATER**¹, **Y. GRANT**¹, **T. DICKERSON**², **M. TAFFE**¹

¹Neurosci., ²Chem., The Scripps Res. Inst., La Jolla, CA

Abstract: Rationale:

First emerging prominently onto the recreational drug scene in the mid-to-late 2000s, synthetic cathinones (often generically referred to as “bath salts”) continue to be abused throughout much of Europe and North America. Today, several generations of synthetic cathinones have been identified among samples seized by law enforcement and in emergency room toxicology reports. New variants of these drugs have appeared with regular frequency in an apparent attempt by illicit manufacturers to circumvent changing drug laws. Many of these variations consist of *4-methyl* and *3,4-methylenedioxy* substitutions to the aromatic ring of a parent synthetic cathinone compound. Intravenous self-administration (IVSA) is a widely accepted paradigm for assessing the reinforcing characteristics and abuse liability of psychoactive substances. The present study utilized an IVSA procedure in rats to elucidate alterations in reinforcing efficacy and potency that may be conferred by the *4-methyl* and *3,4-methylenedioxy* substitutions.

Methods:

Male and female adult Wistar rats were trained to self-administer α -pyrrolidinovalerophenone (α -PVP; 0.05 mg/kg/infusion) or 3,4-methylenedioxypropylvalerone (MDPV; 0.05 mg/kg/infusion) under a fixed-ratio 1 (FR1) schedule of reinforcement during daily 60-minute sessions. Following acquisition, dose-response curves were generated for MDPV, α -PVP, 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylcathinone (ethylone), 4-methylethcathinone (4-MEC), 3,4-methylenedioxymethylcathinone (methyline), and 4-methylmethcathinone (mephedrone).

Results:

Results indicate that the *4-methyl* and *3,4-methylenedioxy* substitutions do not alter the potency and efficacy as reinforcers in a consistent manner.

Conclusion:

While some structure-activity relationships may exist between ring substituted and the related unsubstituted synthetic cathinones, differences in reinforcing potency and efficacy suggests that individual characterization of each new substance is required for full understanding.

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Poster

079. Behavioral Studies of Amphetamines

Location: SDCC Halls B-H

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Program #/Poster #: 079.26/DDD14

Topic: G.08. Drugs of Abuse and Addiction

Support: DA 10344

DA 31246

DK 096983

ODP 51011132

Title: Serotonin 5-HT_{2C} receptor modulation of compulsive and addictive behavior in female rhesus macaques

Authors: *M. PEREZ DIAZ^{1,2}, M. E. WILSON², L. L. HOWELL²

¹Psychiatry, UCLA, Los Angeles, CA; ²Yerkes Natl. Primate Res. Ctr., Emory Univ., Atlanta, GA

Abstract: Addiction is a significant public health issue, yet there are limited FDA-approved treatments for certain addictive disorders and none for addiction in general. Identifying the core behavioral and neurochemical processes contributing to an addictive phenotype can inform the development of novel therapeutics to treat multiple addictions. Compulsivity is highly implicated in the etiology of addiction and greater among addicted individuals than controls. Despite this evidence, the effect of engaging in addictive behavior on compulsivity has not been tested. Although studies provide evidence that serotonin 5-HT_{2C} receptors are involved in the expression of both compulsive and addictive behaviors, the extent to which these behaviors are regulated in parallel is unknown and the exact effects of 5-HT_{2C} receptors on compulsivity remain unclear. Therefore, we employed two reinforcers, a high caloric diet (HCD) and methamphetamine (METH), to investigate the effects of long-term reinforcer intake on general compulsive behavior in female rhesus macaques. In addition, we evaluated the effects of a 5-HT_{2C} receptor agonist, WAY163909, on baseline compulsivity, compulsivity following long-term reinforcer intake, drug intake and drug-seeking of METH, and intake of two different diets. Extended intake of METH or a HCD increased general compulsive behavior. Baseline compulsive behavior was not predictive of future METH or HCD intake, but intake of these reinforcers was predictive of post-reinforcer increased compulsivity. WAY163909 decreased compulsivity (at baseline and after long-term reinforcer intake) and intake of a HCD. These effects were blocked by the 5-HT_{2C} receptor antagonist SB 242084, demonstrating that the 5-HT_{2C} receptor is necessary for the effects of WAY163909. WAY163909 also decreased METH intake and METH-induced reinstatement, as well as METH-induced dopamine overflow in the nucleus accumbens. These findings are important because they provide evidence that (1) long-term intake of a drug or food reinforcer increases compulsivity, with the amount of reinforcer intake being predictive of the increase in compulsivity, and (2) 5-HT_{2C}Rs play a crucial role in both compulsivity and reinforcer intake, as activation of these receptors decreases both measures, regardless of the reinforcer or whether compulsivity is measured at baseline or after prolonged intake of reinforcers. As a whole, the results suggest that agonists at the 5-HT_{2C}R may represent a promising new avenue for treatment of addiction in general, especially if these findings can be expanded upon to demonstrate efficacy with other types of reinforcers and reinforced behaviors.

Disclosures: M. Perez diaz: None. M.E. Wilson: None. L.L. Howell: None.

Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 080.01/DDD15

Topic: G.08. Drugs of Abuse and Addiction

Support: DA033436

Title: Ceftriaxone attenuates cued cocaine-seeking after abstinence

Authors: *L. A. KNACKSTEDT¹, C. N. LOGAN², Y. PADOVAN-HERNANDEZ³, A. R. BECHARD³

¹Psychology, ²Psychology Dept., ³Univ. of Florida, Gainesville, FL

Abstract: Cocaine use disorder is characterized by compulsive drug use and periods of abstinence interspersed with relapses. Drug-associated cues and contexts maintain conditioned reinforcing properties that trigger relapse. Our lab uses a rat model of cocaine self-administration and relapse and has found that impaired glutamate homeostasis mediates relapse to cocaine-seeking. Ceftriaxone, a β -lactam antibiotic, restores glutamate homeostasis that is impaired by chronic cocaine self-administration. Subchronic treatment with ceftriaxone reduces cocaine-seeking during context-, cocaine- and cue-primed tests of relapse. Glutamate release in the nucleus accumbens (NA) core drives reinstatement and ceftriaxone prevents this release during cocaine-primed reinstatement after instrumental extinction. However, we have shown that in the absence of instrumental extinction, ceftriaxone is unable to prevent glutamate efflux in the NA core during context-primed relapse to cocaine-seeking. Post-drug experience (abstinence vs. extinction) alters glutamatergic adaptations in the NA after cocaine. It is also known that different brain regions mediate relapse primed by different stimuli (e.g. cue vs. context). Here, we investigated whether extinction training is required for ceftriaxone to prevent glutamate efflux when cocaine-associated cues are used to prime relapse. We also assessed Fos expression in regions known to mediate cocaine relapse to test the hypothesis that ceftriaxone would attenuate neuronal activation throughout this circuitry. We found that in the absence of extinction training, ceftriaxone reduced cue-primed cocaine relapse and the associated glutamate efflux in the NA core. We found that ceftriaxone increased Fos expression in the infralimbic cortex and Fos expression in this region negatively correlated with lever pressing during reinstatement. These data support the ability of ceftriaxone to attenuate relapse and glutamate efflux in the NA core in the absence of extinction training and a role for infralimbic neurons in doing so.

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 080.02/DDD16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA041455
NIH Grant DA007244

Title: Effects of nicotinamide on cocaine reinstatement

Authors: *E. A. WILLIAMS, K. J. REISSNER

Behavioral and Integrative Neurosci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Accumulating evidence indicates that prolonged abstinence following drug self-administration leads to communication impairments between astrocytes and neurons within the nucleus accumbens (NAc). For example, astrocytes exhibit reduced synaptic colocalization in the NAc following cocaine self-administration and extinction, as well as deficits in glutamate uptake and release. These changes may impact their role of astrocytes in providing metabolic support via coupling of synaptic activity with vascular glucose through endfeet. Neurons and astrocytes have complementary metabolic profiles such that neurons preferentially use lactate for energy support while astrocytes preferentially uptake glucose. Glucose from blood is converted to lactate in astrocytes prior to transport into neurons for energy utilization, but release large amounts of lactate to be taken up by neurons for energy utilization: referred to as the astrocyte-neuron lactate shuttle. The conversion of glucose to pyruvate and subsequently to lactate, which is then converted to lactate, requires two NAD⁺ molecules per glucose molecule. Enzymes, such as PARP-1, also consume NAD⁺ and are found to be upregulated following cocaine self-administration. Thus, we hypothesized that cocaine self-administration and extinction creates strain on NAc NAD⁺ levels and regulation of cellular energetics. The goal of our study is to investigate the effects of systemic nicotinamide (NAM), the main niacin-derived NAD⁺ precursor, on reinstatement to cocaine seeking following self-administration and extinction and on the cellular adaptations induced by cocaine and believed to mediate reinstatement. We hypothesized that NAM administration during extinction would increase available NAD⁺, leading to reduced reinstatement. Male Sprague-Dawley rats were trained to self-administer i.v. cocaine for 2hrs per day for 12 days followed by 14-17 days of extinction, during which i.p. NAM injections were given 30 minutes prior to each session. Rats were then tested on both cue and cocaine reinstatement as well as locomotor activity. Chronic NAM administered throughout extinction dose-dependently attenuated reinstatement, with no effect on extinction responding. In contrast, acute NAM given once prior to reinstatement tests had no effect. While chronic NAM had no effect on locomotor activity in an open field, it did reduce

cocaine-induced locomotor activity. Ongoing studies will examine the effect of chronic NAM on reinstatement to food seeking, as well as mechanisms by which NAM reduces reinstatement to cocaine seeking.

Disclosures: K.J. Reissner: None.

Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 080.03/DDD17

Topic: G.08. Drugs of Abuse and Addiction

Support: DA033436

Title: Ceftriaxone increases surface mGlu2 expression in male and female rats

Authors: *C. N. LOGAN¹, P. U. HAMOR², M. SCHWENDT², L. A. KNACKSTEDT²

¹Psychology Dept., ²Univ. of Florida, Gainesville, FL

Abstract: The prevention of relapse is a significant challenge in the treatment of cocaine addiction. Our lab uses a rodent model of operant cocaine self-administration to identify neuroadaptations occurring after a drug-free period of 2-3 weeks to drive relapse to cocaine seeking in the extinction-reinstatement model. We have found that at this time, expression and function of the glutamate transporter GLT-1 is decreased in the nucleus accumbens core (NAc). The β -lactam antibiotic ceftriaxone has been proposed as a potential treatment for cocaine relapse as it attenuates the reinstatement of cocaine-seeking and restores GLT-1 expression and function. We have previously demonstrated that GLT-1 upregulation in the NAc is necessary for ceftriaxone to attenuate reinstatement. However, we recently found that AAV-mediated GLT-1 overexpression in the NAc was not sufficient to attenuate cue- or cocaine-primed reinstatement of cocaine-seeking. GLT-1 overexpression attenuated, but did not prevent, glutamate efflux during reinstatement. Thus, here we test the alternative hypothesis that Cef also works to attenuate glutamate efflux through the presynaptic mGlu2/3 autoreceptor in the NAc. Male and female rats self-administered cocaine for 12 days, followed by extinction training. Estrous cycles were tracked in female rats. Rats were sacrificed after 2-3 weeks of extinction and a biotinylation assay performed on fresh NAc tissue. Western blots for mGlu2 were performed. In a separate group of rats, we examined the role of mGlu2/3 activation on ceftriaxone's ability to attenuate reinstatement by infusing the mGlu2/3 antagonist LY341495 into the NAc immediately prior to a reinstatement test. We found that in both male and female rats, surface mGlu2 was reduced by cocaine and restored by ceftriaxone. We found no effects of estrous cycle phase on mGlu2 expression. Preliminary work indicates that in mGlu2/3 antagonism in the NAc prevents ceftriaxone from attenuating cue primed-reinstatement of cocaine-seeking. This work indicates

that the ability of ceftriaxone to attenuate reinstatement and the NAc glutamate efflux that accompanies it depends on mGlu2/3 function and possibly upregulation.

Disclosures: C.N. Logan: None. P.U. Hamor: None. M. Schwendt: None. L.A. Knackstedt: None.

Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 080.04/DDD18

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01 DA034684

Title: When to seek and when to stop: Changes in infralimbic cortical neuronal activity during the suppression of cocaine-seeking behavior

Authors: *V. A. MULLER EWALD¹, R. T. LALUMIERE²

²Dept. of Psychological and Brain Sci., ¹Univ. of Iowa, Iowa City, IA

Abstract: Prior work has implicated the infralimbic cortex (IL) in the consolidation of extinction learning following cocaine self-administration. However, most studies investigating this role for the IL employ *manipulations* of this cortical region, and little work has *recorded* IL activity during the extinction of cocaine seeking. To determine how IL activity relates to the extinction of cocaine-seeking behavior, we used *in vivo* electrophysiology to record from the IL of behaving rats as they underwent extinction training. Male Sprague-Dawley rats (250 - 275 g) underwent surgery for intravenous catheter implantation, followed by cocaine self-administration for a minimum of 15 consecutive d. During self-administration, a light signaled the beginning of a 30 s availability period, during which a lever press was rewarded with a cocaine infusion, followed by immediate retraction of the lever and an intertrial interval. If animals failed to respond within the availability period, the lever was retracted and intertrial interval ensued. When animals showed stable performance on the task, a fixed 9-channel electrode array was implanted aimed at the IL. Animals were then re-trained on the task and underwent extinction training for a minimum of 8 d. Extinction involved the same behavioral paradigm as self-administration, however, lever presses did not produce cocaine infusions. During extinction training, recordings were conducted every day, and data were analyzed for the early, middle and late extinction time points. Findings indicate that a subpopulation of IL units is responsive to non-rewarded lever presses, in accordance with prior studies. Results also indicate the existence of units that are responsive to the onset of the availability signal. A subset of these particular units modulate their firing at the presentation of the availability signal in a manner predictive of the later occurrence or absence of a lever press. Finally, IL units show changes in firing dynamics, such as increases

in baseline firing rates and burst firing during the progression of extinction training, as animals learn to withhold lever pressing. These findings suggest the existence of different IL neuronal sub-populations that include pre-motor neurons, neurons responsive to environmental cues, and neurons responsive to behavioral events. Furthermore, patterns of firing in these neurons change as animals learn to withhold lever pressing during extinction training. Together with prior work using brain-based manipulations, these findings suggest that IL activity guides behavioral outcomes during extinction of cocaine-seeking behavior.

Disclosures: V.A. Muller Ewald: None. R.T. LaLumiere: None.

Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

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Program #/Poster #: 080.05/DDD19

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA15758 to John Mantsch (JM)
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Title: Role of endocannabinoid signaling in the ventral tegmental area and nucleus accumbens shell in chronic electric footshock stress-induced escalation of cocaine intake in rats

Authors: *R. SCHAPS¹, J. R. MCREYNOLDS², C. P. WOLF², D. S. STARCK², C. J. HILLARD³, J. R. MANTSCH²

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Abstract: Stress is an important contributing factor to addiction and is problematic as stress is unavoidable in daily life. Addiction can be characterized by a loss of control over drug intake that is modeled by escalating patterns of drug self-administration (SA). We have previously shown that a stressor, electric footshock stress, administered daily at the time of SA induces an escalation of cocaine intake in rats that would otherwise demonstrate stable cocaine SA under short-access conditions (2-h/day). Stress-induced escalation of SA is likely the consequence of neuroplastic changes that involve neurobiological mediators that connect stress-responsive and reward systems in the brain, such as the endocannabinoid system (eCB). These changes likely occur in regions implicated in both stress and reward, such as the nucleus accumbens shell (NAc) and ventral tegmental area (VTA). We hypothesize that repeated stress at the time of SA induces a persistent increase in eCB signaling, in the NAc shell and VTA, that results in escalation of cocaine use and increased susceptibility to later reinstatement. Male SD rats were trained to SA cocaine (0.5 mg/kg/inf) on a FR 4 schedule in 4 X 30 min SA sessions separated by 5-min drug-free periods. Some rats received shock in the SA chamber during the 5 min drug-free period over

14 days. Systemic administration of the CB1R antagonist AM251 (1 mg/kg) prior to the SA session attenuated cocaine intake only in stress-escalated rats. Intra-NAc shell administration of AM251 (1, 3 µg) attenuates cocaine intake only in stress-escalated rats. Surprisingly, intra-VTA administration of AM251 (1, 3 µg) prior to the SA session appears to attenuate intake in non-escalated rats though there is greater attenuation of cocaine intake in stress-escalated rats. Studies examining CB1R density in the NAc shell and VTA following SA under stress and non-stress conditions are ongoing. These data suggest that repeated stress recruits eCB signaling in the NAc shell and VTA to drive drug use. Separate groups of rats were tested for reinstatement of drug-seeking behavior to a priming injection of cocaine (2.5, 5, or 10 mg/kg). Rats who received shock during SA demonstrated augmented reinstatement to all doses of cocaine. Furthermore, as with SA, the CB1R antagonist AM251 given prior to injection of cocaine (10 mg/kg, ip) significantly attenuated cocaine-primed reinstatement only in stress-escalated rats. These data suggest that stress-induced neuroplastic changes occur, likely in the eCB system, in regions of the brain that influence expression of escalated cocaine intake and augmented cocaine-primed reinstatement and these changes may be glucocorticoid-dependent.

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

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Program #/Poster #: 080.06/DDD20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA15758
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Title: Prelimbic cortical estrogen receptor contributions to 17β-estradiol-potentiated reinstatement of cocaine seeking behavior in female rats

Authors: ***C. KONRATH**¹, E. M. DONCHECK¹, M. C. DEBAKER¹, G. T. LIDDIARD¹, L. YU², L. A. URBANIK¹, L. M. BARRON¹, J. J. TUSCHER³, K. M. FRICK³, M. C. HEARING¹, Q.-S. LIU², C. J. HILLARD², J. R. MANTSCH¹

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Abstract: Although peak physiological levels of estrogens correspond to enhanced relapse vulnerability in female cocaine addicts, the underlying mechanisms are not well understood. We recently developed a new preclinical self-administration model to study this phenomenon, in

which sexually mature ovariectomized female rats given proestrus levels of the primary estrogen 17 β -estradiol (E2; 10 μ g/kg, i.p., 1-hr pretreatment) exhibit potentiated reinstatement of cocaine-seeking behavior in response to an ordinarily subthreshold dose of cocaine (1.25 mg/kg). We localized the potentiating effects of E2 to the prelimbic prefrontal cortex (PrL), as intra-PrL application of E2 (5 μ g/0.3 μ L; 15-min pretreatment) reproduced the potentiation effect. Using this model, we now find the potentiating effects of E2 on responding to subthreshold cocaine can be reproduced by systemic activation of estrogen receptor- β (ER β ; 1 mg/kg DPN, i.p., 30-min pretreatment), but not estrogen receptor- α (ER α ; 1 mg/kg PPT, i.p., 30-min pretreatment). We similarly find the potentiating effects of ER β activation can be localized to the PrL, as intra-PrL ER β activation is both necessary (100 ng PHTPP/0.3 μ L; 15-min pretreatment) and sufficient (100 pg/0.3 μ L DPN; 15-min pretreatment) for potentiated reinstatement. Similar effects on potentiated reinstatement are not observed with PrL ER α , as ER α antagonism (16 μ g MPP/0.3 μ L; 15-min pretreatment) fails to block reinstatement. Ongoing experiments aim to further characterize estrogen receptor contributions to E2-potentiated reinstatement.

Concurrent with these behavioral studies, whole-cell voltage clamp recordings were made in slices from female PrL layer V pyramidal neurons to determine the effects of E2 on PrL neuronal activity. These recordings revealed that E2 (100 nM, 10-min application) enhances the frequency of miniature excitatory postsynaptic currents, suggesting that E2 can act within the PrL to enhance presynaptic glutamate release, an effect elsewhere implicated to be mediated by ER β activation. No effects of E2 on inhibitory postsynaptic current frequency or amplitude were observed.

These results indicate that E2-enhanced reinstatement vulnerability in female rats involves activation of ER β in the PrL, wherein E2 can simultaneously enhance excitatory synaptic activity in layer V pyramidal neurons. Investigations are underway to determine the extent to which these mechanisms may be intertwined.

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Poster

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Support: NIH grant DA038663 to Mantsch and Hillard

Title: Glucocorticoid-endocannabinoid interactions in the prelimbic cortex mediate stress-potentiated reinstatement of cocaine seeking through increased activation of the cortico-accumbens pathway

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Abstract: Even when stress does not directly trigger drug seeking, it can still potentiate responsiveness to other triggers for drug use. We have shown that under conditions where it does not reinstate cocaine seeking, footshock stress potentiates reinstatement when paired with low-dose cocaine. This effect of shock is corticosterone (CORT)-dependent and is mimicked by systemic or intra-prelimbic cortex (PL) CORT administration, indicating that CORT is necessary and sufficient for potentiated reinstatement and that the PL is a critical site of CORT action. Intra-PL administration of CORT:BSA, which prevents entry of CORT into the cell, also potentiates reinstatement to low-dose cocaine, implicating a non-canonical membrane-associated signaling mechanism. We have shown that CORT acts through PL endocannabinoid (eCB) signaling, as intra-PL cannabinoid type-1 receptor (CB1R) antagonism blocks potentiated reinstatement, and that the eCB 2-arachidonoylglycerol (2-AG) likely mediates this effect. 2-AG synthesis can result from Gq-protein signaling, and we found that intra-PL administration of a Gq palpeptide, which prevents Gq-mediated signaling, blocks CORT-potentiated reinstatement. Taken together, these data suggest that CORT potentiates reinstatement through Gq-dependent 2-AG activation of PL CB1Rs. CB1Rs are located primarily on GABAergic interneurons in the PL, and bath application of CORT to nucleus accumbens (NAc) core-projecting pyramidal neurons attenuates inhibitory neurotransmission in a CB1R-dependent manner. Thus, we hypothesize that this CB1R-dependent attenuation of inhibition increases activation of NAc-core-projecting pyramidal neurons to facilitate drug seeking. Utilizing a double label immunohistochemical approach in the PL, we quantified co-expression of a retrograde tracer, CTb, that was injected into the NAc core, and the activity marker Fos following CORT-potentiated reinstatement. Our data suggests there is increased activation of the cortico-accumbens pathway following CORT-potentiated reinstatement, and the contribution of the eCB system to this effect is currently being examined. We are also testing the behavioral relevance of this pathway utilizing an intersectional DREADD viral approach. Preliminary data suggest that inactivation of the cortico-accumbens pathway, via activation of Gi-DREADDs, blocks CORT-potentiated reinstatement. These findings support the hypothesis that CORT acts in the PL through CB1R-mediated inhibition of GABA to facilitate activation of the cortico-accumbens pathway and potentiate cocaine-seeking reinstatement.

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

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NIH Grant DA038663-S1

Title: Stress converges on prelimbic cortical cannabinoid type-1 receptor activation to potentiate cocaine-seeking reinstatement in both sexes: Characterization of sex differences and divergent responding

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Abstract: Although clinical observations imply that female cocaine addicts experience enhanced relapse vulnerability compared to males, particularly within the context of stress, the underlying mechanisms are poorly understood. As we have previously found that stressors and stress-level corticosterone (CORT) can potentiate cocaine-seeking reinstatement vulnerability in male rats through prelimbic cortical (PrL-PFC) cannabinoid type-1 receptor (CB1R) activation, we examined the contribution of biological sex to this phenomenon.

Despite equivocal responding during cocaine self-administration and extinction, a sex difference was observed in the threshold for cocaine-primed reinstatement, with 2.5 and 1.25 mg/kg cocaine (i.p.) identified as subthreshold doses for males and females, respectively. While neither subthreshold cocaine nor stress-level CORT (2 mg/kg, i.p., 40-min pretreatment) alone were sufficient to trigger drug-seeking reinstatement in either sex, pretreatment with CORT significantly potentiated reinstatement responding to subthreshold cocaine in both sexes. Surprisingly, footshock (3 x 0.6 mAmp, 200-ms duration, 45-s avg ITI, 15-min period), which produces robust potentiated reinstatement in males, did not potentiate reinstatement in females at any amperage tested (0.15-0.90 mAmp). However, immobilization-restraint stress (15-min) potentiated reinstatement in both sexes. As in males, the potentiating effects of CORT could be localized to the PrL-PFC in females, as intra-PrL-PFC CORT (50 ng/0.3 μ L, 15-min pretreatment) delivery reproduced the systemic potentiation effect. Furthermore, PrL-PFC CB1R activation was necessary for both CORT and restraint-potentiated reinstatement in females, as both were blocked by intra-PrL-PFC CB1R antagonism (AM251; 300 ng/0.3 μ L, 15-min

pretreatment). Finally, as has also been observed in males, whole-cell patch clamp electrophysiological recordings from layer V PrL-PFC pyramidal neurons revealed CORT application (1 μ M) attenuates inhibitory neurotransmission in a CB1R-dependent manner (AM251; 2 μ M).

Together, these results suggest that stress and CORT can potentiate reinstatement vulnerability in a PrL-PFC CB1R-dependent convergent manner in females as in males. However, females display an enhanced sensitivity to the potentiating effects of stress and CORT due to a reduced threshold for cocaine-primed reinstatement. Finally, the divergent response to footshock suggests that not all stressors act alike in promoting drug-seeking as a coping strategy in both the sexes.

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant DA15758 to JRM

Title: Augmented CRFR1-dependent regulation of a dopaminergic ventral tegmental area to prelimbic cortex projection establishes susceptibility to stress-induced cocaine seeking

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Abstract: The ability of stress to trigger cocaine seeking in humans and rodents is variable and is determined by the amount and pattern of prior drug use. This study examined the role of a corticotropin releasing factor- (CRF-) regulated dopaminergic projection from the ventral tegmental area (VTA) to the prelimbic cortex in shock-induced cocaine seeking and its recruitment under self-administration conditions that establish relapse vulnerability. Rats with a history of daily long-access (LgA; 14 x 6 hrs/day) but not short-access (ShA; 14 x 2 hrs/day) self-administration showed robust shock-induced cocaine seeking that was associated with a heightened shock-induced prelimbic cortex Fos response and activation of VTA neurons

projecting to the prelimbic cortex, as measured using a retrograde tracer combined with a dual-label immunohistochemistry approach. Silencing of these neurons using an intersectional DREADD-based approach prevented shock-induced cocaine seeking upon systemic injections of CNO. As we observed DREADD expression in both TH-positive (~80%) and TH-negative neurons in the VTA, experiments using TH-Cre rats to specifically target the contribution of mesocortical dopamine neurons to stress-induced cocaine seeking are ongoing. Both shock-induced reinstatement and the prelimbic cortex Fos response were prevented by bilateral intra-VTA injections of the CRF receptor 1 (CRFR1) antagonist, antalarmin. Pharmacological disconnection of the CRF-regulated dopaminergic projection to the prelimbic cortex by injection of antalarmin into the VTA in one hemisphere and the D1 receptor antagonist, SCH23390, into the prelimbic cortex of the contralateral hemisphere prevented shock-induced cocaine seeking, while antagonist administration within the same hemisphere or disconnection of the VTA projection to infralimbic cortex was without effect. LgA, but not ShA, cocaine self-administration resulted in increased CRFR1 mRNA levels in the VTA as measured using *in situ* hybridization. Studies using fluorescence-activated cell sorting to quantify changes in CRFR1 expression in subpopulations of VTA neurons according to their projection fields are ongoing. Altogether, these findings suggest that excessive cocaine use establishes susceptibility to stress-induced relapse by recruiting CRF regulation of a mesocortical dopaminergic pathway.

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 080.10/DDD24

Topic: G.08. Drugs of Abuse and Addiction

Title: The role of aversion in cocaine addiction

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Abstract: Over 90% of Americans have had some exposure to drugs of abuse, but only 15-32% of individuals exposed to the major classes of abused drugs go on to become addicted, with the rest presumably being able to stop on their own. Some areas of differential vulnerability could involve differences in initial responses to drugs, in responses to novelty and risk, as well as in the ability to limit intake as the costs of drug use begin to rise. Relatively little is known about these

factors, and much basic research has been directed at understanding individual animals who have already progressed into addiction-like behaviors, with relatively less study of what protective factors may help prevent acquisition of drug use in the first place.

Nonetheless, a number of vulnerability factors have been examined. For example, prior work from Huda Akil and colleagues has shown that locomotor response to novelty is predictive of the rate of acquisition of drug-seeking. However, considerable unexplained variance remains, suggesting that this phenotype is just one of many possible protective elements. We hypothesize that drug-induced aversion is one of the factors that play a major role in drug-resistance.

Although cocaine's aversive responses are relatively less widely acknowledged than its rewarding effects, they are experimentally robust. Particularly elegant experiments by Ettenberg and his group have shown that single doses of cocaine produce an initial rewarding phase followed by an aversive crash about 15' later that is sufficient to condition a net aversion to cocaine, that in most (but not all) animals, is strong enough to overcome cocaine's rewarding effects. In our lab, we found that the aversive effects of cocaine were more individually variable, and much better predictors of cocaine-seeking, than the rewarding effects. We have shown that cocaine avoidance is protective of drug acquisition on self-administration, but is also highly predictive of reinstatement.

In recent years, our lab and others have demonstrated that cocaine avoidance depends critically on the rostromedial tegmental nucleus (RMTg) and its afferents. The RMTg is a major GABAergic midbrain input to midbrain dopamine (DA) neurons that plays major roles in avoidance. We have thus shown that there are individual differences in RMTg neurons firing rate that correlate with cocaine-conditioned avoidance behavior. Indeed, compared to low cocaine avoiders, high avoider animals have similar RMTg inhibition during the rewarding phase of the drug (5' post injection), but have significantly higher RMTg firing rates during its aversive phase (15' post-infusion).

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

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Title: Neural substrates associated with reduction in expression of cocaine conditioned place preference by transdermal cannabidiol

Authors: *G. E. WAGNER¹, G. DE NESS¹, A. LAQUE¹, H. NEDELESCU¹, A. CARROLL¹, T. KERR¹, D. WATRY¹, M. W. BUCZYNSKI², N. SUTO¹, F. WEISS¹

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Abstract: We determined the effects of transdermal cannabidiol (tCBD) against the expression of cocaine conditioned place preference (CPP) as a model of cocaine-seeking and relapse. Male Wistar rats were trained to distinguish two distinct environmental contexts: one of the contexts was paired with cocaine (15 mg/kg, IP), while the other context was paired with saline (0.5 ml, IP). The rats then were randomly assigned to six experimental groups defined by the dose of tCBD (0.0, 2.5, 5.0, 7.5, 10 and 15 mg/kg) and treated with tCBD once daily for four days. Rats treated with 5.0 and 7.5 mg/kg of tCBD did not show a significant preference to either context. On the fourth day of tCBD treatment, the rats were tested for cocaine CPP. Rats treated with vehicle (tCBD: 0.0 mg/kg) spent significantly more time in the cocaine-paired context than the saline-paired context. Similar results were obtained in rats treated with 2.5, 5.0 and 15 mg/kg of tCBD demonstrating a u-shaped dose-response profile. This reduction in CPP was associated with a significant reduction in neural activation (as measured by the activation marker Fos) within the prelimbic cortex - a brain region implicated in drug relapse. In contrast, tCBD produced no significant effect in the adjacent infralimbic cortex or the nucleus accumbens core/shell. Consequently, tCBD - at specific doses - may serve as an effective anti-relapse treatment via inhibiting normally drug cue-reactive neurons in a specific brain site. Ongoing experiments will establish the effects of tCBD on normally drug cue-reactive neural phenotypes and neurochemicals. The results of these studies will further characterize the brain mechanisms underlying the promising action of tCBD against drug relapse.

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Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

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Title: A prefronto-habenular circuit involved in stress-induced reinstatement

Authors: *V. MATHIS^{1,2}, S. P. B. CALIGIURI², C. FILLINGER², P. J. KENNY³

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Abstract: Our ability to cope with a situation and to adapt our behavior is essential for our well-being, social integration, and survival. A deficit in these complex capabilities, requiring high-order brain functions such as memory, anticipation, planification and execution of plans, may lead to severe behavioral disorders. Indeed, several pathologies such as addiction, depression, eating disorders or autism for instance are characterized by a deficit in our behavioral adaptation. This capacity is even more important when we are confronted with a stressful situation. Indeed, stress is one of the major precipitating factor of numerous pathologies among those cited above and is well known to contribute to addiction relapse. Unfortunately, the cerebral network involved in our capacity to adapt our behavior remains to be well characterized. Recent works suggest that the lateral habenula (LHb) may play a critical role in such a function. Indeed, this diencephalic well-conserved structure was described as implicated in reward-based and memory-based behaviors. Moreover, it participates in the integration of the emotional valence of a situation. It has also been recently described that the LHb activity is altered by cocaine intake or even after the cessation of cocaine intake. More precisely, after a cocaine withdrawal period, the LHb is hyperactive and this mechanism could be responsible of the aversive effect seen in cocaine abstinent inpatients and animal models of addiction. Thus, the LHb seems to play a major role in our ability to adapt our behavior; cocaine-induced alterations of the LHb activity may lead to a disruption of this ability and finally conduct to relapse. Here we investigated the potential role of the LHb as well as the network in which it belongs in stress-induced reinstatement (SIR). Using a combination between retro-AVV tracing, targeting the LHb and the ventral tegmental area (VTA), and a CPP protocol for cocaine, we mapped the LHb network in regard to the dopaminergic system involved in the SIR. Mice underwent a conditioning for cocaine (20mg/kg) for 5 days, followed by an extinction phase. Then, mice underwent a yohimbine injection (5 min before the test, 15mg/kg) in order to induce a reinstatement. Ninety minutes after the SIR protocol, mice were sacrificed and C-fos immunostaining performed. The co-localization of the different retro-AAVs and the C-fos uncovers an interesting circuit comprising the medial prefrontal cortex (mPFC), the LHb and the VTA, involved in the SIR. These results suggest that a complex mPFC-LHb-VTA network, likely controlling the VTA dopamine release, is involved in stress-induced reinstatement.

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Poster

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Ron and Pratima Gatehouse Trust Fund
Anne and Phillip Glatfelter III Family Foundation

Title: Chronic high exposure to cocaine results in degeneration of VTA dopaminergic neurons

Authors: *K. VENKITESWARAN, M. SUBRAMANIAN, T. CAYTON, A. KIM, P. S. GRIGSON, T. SUBRAMANIAN
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Abstract: Understanding the neurobiological mechanisms is important to develop experimental therapeutics for treatment-resistant drug addiction. Recent experiments have shown that optogenetic stimulation of Ventral Tegmental Area - Nucleus Accumbens (VTA-NAc) pathway is sufficient to elicit increased drug seeking behavior seen in cocaine self-administering animals, proving the pre-eminence of this dopaminergic pathway in the pathogenesis of cocaine addiction. Human autopsy studies show that chronic large cocaine abuse results in mid-brain dopaminergic neuronal loss. We hypothesized that dopaminergic neuronal loss in high-drug taking rats will be specific to VTA-NAc dopamine neurons sparing other CNS dopaminergic systems. A total of 126 rats were operant conditioned to self-administer cocaine using a FR10 and FR20 training scheme. Animals split themselves into high drug taking and low drug taking animals. Behavioral testing and other experimental details of these cohort has been previously published (Venkiteswaran, et. al., 2016). These animals did not exhibit any features of parkinsonism suggesting that there was no loss or deficits in the SNpc-dorsal striatum dopaminergic pathway. The animals were euthanized 90-120 days after their last exposure to cocaine self-administration. We undertook a detailed design-based unbiased stereological evaluation of VTA and SNpc tyrosine hydroxylase positive (TH+) cell bodies using optical fractionator probe. High dose cocaine-self-administering rats showed a statistically significant reduction of TH+ cell bodies in VTA (>50% loss) whereas the SNpc TH+ neurons showed no statistically significant loss. Low drug taking animals and control animals showed no significant loss of TH+ neurons. In an in

vitro experiment, culture of dissociated fetal ventral mesencephalic tissue single cell suspension were exposed to increasing concentrations of cocaine to simulate the in vivo paradigm. These experiments showed that TH+ neurons were reduced in a dose responsive fashion to cocaine exposure. Controls obtained from fetal dorsal mesencephalic, lateral ganglionic eminence (LGE), cerebellar and cortical progenitors did not show dose responsive loss of TH+ neurons. No nonspecific toxicity were noted in these culture studies indicating a specific loss of dopaminergic neuronal loss. In vitro cell count was performed using design based 2D stereology and petrimetrics to avoid bias. Our in vitro and in vivo findings suggest that the neurotoxicity associated with chronic high exposure to cocaine is specific to VTA dopaminergic neurons and spares the adjacent SN dopaminergic neurons.

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Poster

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Michigan State University MS100332

Title: Context-associated cocaine use during adolescence: Effect on context-induced reinstatement during adulthood

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Abstract: Key Words: self-administration, adolescent, context-induced reinstatement
Cocaine use disorders are characterized by a high risk of repeated relapse following periods of abstinence. Relapse can occur following exposure to stressful events, explicit drug cues or environmental contexts that were previously associated with drug taking. The neural mechanisms contributing to these strong drug-context-associations have been investigated using adult rodent models of relapse. Drug use is often initiated at adolescence and therefore it is important to understand how drug taking during this critical developmental window may affect drug-seeking behavior during adulthood. Previous research has shown that rats which self-administered cocaine during adolescence display increased drug-primed and stress-induced (but not cue-induced) reinstatement of drug-seeking behavior as adults. The role of contextual stimuli in this phenomenon is unknown;

therefore, we aim to examine whether cocaine-context associations formed during adolescence can evoke drug-seeking behavior during adulthood. Additionally, we examined whether single or pair-housing conditions would influence context-induced reinstatement.

Male, sprague-dawley rats (Envigo, postnatal day 30 (P30) on arrival), received jugular catheterization surgery at P35-37. Following surgery and recovery, rats were either pair or single housed. At P40-42, rats began self-administration training (distinct contextual environment, FR1 schedule of reinforcement, minimum of 10 days) followed by extinction training (separate, distinct context, minimum 7 days). Drug-seeking behavior (i.e. active lever presses) was examined during a two-hour reinstatement test in the previously cocaine-paired context. We found that exposure to a context that was previously associated with drug taking during adolescence, elicited future drug-seeking behavior. No differences in reinstatement behavior were observed between housing conditions. These results indicate that environmental stimuli associated with adolescent drug use can later potentiate relapse in adulthood.

Disclosures: **A. Bal:** None. **R.M. Butler:** None. **S. Varatharajan:** None. **M. Verma:** None. **A.A. Arguello:** None.

Poster

080. Drugs of Abuse and Addiction: Cocaine Seeking and Reinstatement I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 080.15/EEE5

Topic: G.08. Drugs of Abuse and Addiction

Support: CAPES Fellowship
FAPESP 2013/24986-2

Title: Neuronal ensembles molecular adaptations induced by incubation of cocaine craving

Authors: ***A. ANESIO**, T. S. YOKOYAMA, S. A. ENGI, F. C. CRUZ
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Abstract: Once established, cocaine addiction is a long-lasting condition, in which individuals experience intense craving and a higher risk of relapse even after prolonged periods of abstinence. One of the most recent theory of drug addiction postulates that drug addiction involves associative learning behaviors. According to this theory, the exposure to environmental stimuli previously associated with drug use promote craving and may lead to relapse. In this context, it has been demonstrated that neuronal ensembles encode associative learning related to drug use. Further, studies have demonstrated drug-induced or cue-induced molecular and cellular alterations in the minority of activated neurons or neuronal ensembles, which presumably mediate drug-seeking behaviour and conditioned drug effects. Evidence show that neuronal adaptations related to drug addiction are modified during abstinence period and these

modifications appear to be the neurobiological substrate for increasing cue-induced cocaine craving. This phenomenon is termed incubation of drug craving. Despite of the previous considerations, the vast majority of studies on molecular and synaptic plasticity mechanisms of drug craving assess drug- or cue-induced molecular and cellular alterations in randomly selected neurons independently of their activation state. Therefore, the aim of this study is to investigate molecular adaptations related to incubation of craving in neuronal ensembles selectively activated by cocaine-related cues. Here, we show results from our pilot studies. Male Wistar rats were used. For intravenous cocaine self-administration, right jugular vein was catheterized. Rats were trained to self-administer cocaine for 12 days, 6h/day in a specific context and infusions were paired with a tone-light cue. Then, the effect of exposure to cocaine related cues/context on lever presses was assessed after 1 or 30 withdrawal days. We found that the number of presses in active lever was significantly higher after 30 days of withdrawal than 1 day of withdrawal (20 ± 6 presses/30 min and 2 ± 1 presses/30 min, respectively, $p < 0.05$). Our results demonstrated the incubation of cocaine craving. Next, we will assess molecular adaptations related with incubation of cocaine craving present in selectively activated neuronal ensembles by mass spectrometry.

Disclosures: A. Anesio: None. T.S. Yokoyama: None. S.A. Engi: None. F.C. Cruz: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.01/EEE6

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust NIH Fellowship (C.D.M.)
NIH Grant ZIA MH002928-01

Title: Task representation & learning in prefrontal cortex & striatum as a dynamical system

Authors: *C. D. MÁRTON^{1,2}, D. DURSTEWITZ³, S. SCHULTZ¹, B. B. AVERBECK²
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Abstract: The brain is a non-linear dynamical system and approaching neural processing using methods from dynamical systems is beginning to change our understanding of how areas like prefrontal cortex carry out complex cognitive tasks. Recurrent networks have been used successfully to probe neural population dynamics in simple tasks (Gallego, J. A. et. al. (2017) Neuron 94:978-984; Mante, V. et. al. (2013) Nature 503:78-84; Chaisangmongkon, W. et. al. (2017) Neuron 3 (6):1504-1517). Once trained, artificial network behavior can be compared to

neural recordings in terms of dynamical portraits which can offer insight into how a task is being represented (and solved) in neural space. We trained a recurrent network on a complex learning task involving 8 movement-sequences composed of 3 movements each. Two macaque monkeys executed the same task while recordings were made from lateral prefrontal cortex (IPFC) and dorsal striatum (dSTR) (Seo, M. et. al. (2012) Neuron 74: 947-960). The trained network learned to represent these sequences as distinct, non-overlapping trajectories in neural activation space. Analyzing the dynamical landscape during task execution, we found that the task is represented using distinct fixed points for each task period. We also found that uncertainty during learning is expressed in the network's gradient manifold - as learning progresses, sequence-specific gradient manifolds become more distinct from each other and, hence, more likely to push the network into the correct sequence-specific trajectory. We analyzed spike trains from IPFC and dSTR of two macaques engaged in the same task. We found that movement-sequences are represented as distinct trajectories in the neural population space of both regions. The findings suggest IPFC and dSTR have similar representations of task dynamics at the neural population level - representations that are analogous to those emerging from recurrent neural network simulations of the same task. We show that IPFC and dSTR represent tasks as a dynamical system and that task learning happens by shaping gradient manifolds.

Disclosures: C.D. Márton: None. D. Durstewitz: None. S. Schultz: None. B.B. Averbeck: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.02/EEE7

Topic: H.01. Animal Cognition and Behavior

Title: Spatial and temporal complexity of mouse cortex electrical signalling

Authors: M. LIU¹, Y. LIANG¹, C. SONG², *T. KNOPFEL³, C. ZHOU¹

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Abstract: Brain functions are associated with complex signals across a wide range of spatial and temporal scales, and analysis of measures of brain signal complexity attracted recent attention as markers of intelligence, cognitive states, and brain disorders. Existing technologies to measure brain signals often have limited resolutions either in space (e.g., EEG) or in time (e.g., fMRI) and cannot simultaneously capture both spatial and temporal complexity, so the relationship between these domains remains elusive. New optical voltage imaging methods using genetically encoded voltage indicators provide opportunities to directly observe brain voltage activity across the whole cortex at both high spatial and temporal resolutions. Using cortex-wide imaging data

obtained in mice waking from anesthesia, we explored the relationships between Regional Entropy (spatial complexity) and Multi-Scale Entropy (temporal complexity) of cortical voltage activity. Interestingly, the two measures showed obvious positive and negative correlations at small and large temporal scales respectively, and the robustness of these relationships is confirmed in temporally down-sampled and filtered data, to approximate situations of fMRI-based and EEG-based studies. We further reveal that the temporal and spatial complexities are respectively associated with the heterogeneity of effective temporal and spatial frequencies across the cortical regions. Our work provided new insights and help to unite two opposing viewpoints that suggested that either spatial or temporal complexity is a more informative marker of the underlying neural dynamics. This knowledge also paves the path for studying the relationship between brain signal variability and brain functions in healthy and diseased states using widely available brain imaging technologies despite their limited resolution either in space or time.

Disclosures: M. Liu: None. Y. Liang: None. C. Song: None. T. Knopfel: None. C. Zhou: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.03/EEEE8

Topic: H.01. Animal Cognition and Behavior

Support: Simons Foundation
R01-MH109180
Pew Scholarship in Biomedical Sciences

Title: Structured correlations of neuronal activity within and between regions of primate frontoparietal cortex

Authors: *M. L. WASKOM, B. PURCELL, R. KIANI
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Abstract: Temporal correlations in spontaneous neural activity exhibit structure at multiple spatial scales and provide a powerful tool for understanding the functional organization of cortex. Correlated fluctuations in the hemodynamic signal measured with fMRI have been used extensively to study the large-scale organization of the primate brain, an effort that has identified multiple distributed systems in association cortex. Typically characterized in task-free “resting-state” acquisitions, the large-scale spontaneous correlation structure persists in background activity during task performance and is recapitulated in the functional similarity of task-evoked responses. While these phenomena have captured substantial interest, the limited spatiotemporal resolution of fMRI measurements obscures their neurobiological origin. Are they related to

neuronal spiking? Spontaneous spiking activity in pairs of single neurons can also exhibit structured correlations, but previous electrophysiological investigations of correlation structure have mostly focused within isolated regions, typically in sensory cortex. To draw a closer comparison between the two measurement modalities, we used multi-electrode arrays to simultaneously record from populations of neurons in multiple association regions of two macaque monkeys. We recorded from dorsolateral prefrontal cortex, supplementary eye fields, and intraparietal sulcus both during passive resting-state periods and while the monkeys performed a decision-making task with perceptual and executive components. To characterize the structure of the neuronal activity, we examined spike count correlations between pairs of units across different task phases. While spike count correlations were generally higher within the same area, consistent with the idea that patterns of local correlations can be used to parcellate cortex, positive correlations were also observed between distinct cortical regions. Neither the within- nor between-region correlations were homogeneous; instead, each exhibited structure that was largely stable across distinct task phases and shared between task-engaged and resting states. These results indicate that similar principles govern functional connectivity across multiple spatial and temporal scales, providing new insight into the origin of phenomena that are central in guiding efforts to understand the functional organization of cortex.

Disclosures: **M.L. Waskom:** None. **B. Purcell:** None. **R. Kiani:** None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.04/EEE9

Topic: H.01. Animal Cognition and Behavior

Support: ERC NeuroConsc

Title: Resting-state dynamics as a cortical signature of anesthesia

Authors: ***L. UHRIG**^{1,2}, J. SITT³, A. JACOB¹, J. TASSERIE¹, P. BARTTFELD¹, M. DUPONT¹, S. DEHAENE^{1,4}, B. JARRAYA^{1,5}

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³INSERM, U1127, ICM, Paris, France; ⁴Collège de France, Paris, France; ⁵Foch Hospital, Paris-Saclay Univ., Versailles, France

Abstract: The mechanism by which anesthetics induce a loss of consciousness remains a puzzling problem, because many different anesthetic agents suppress consciousness while acting through different molecular mechanisms. Here, we propose that the common neural mechanism of anesthesia should be sought for at the level of global cortical dynamics (brain function) as compared to its underlying anatomical organization (brain structure). By applying a dynamic

approach to resting-state functional MRI analysis, we previously demonstrated that consciousness emerges from brain functional states that are uncorrelated to the underlying anatomical structure (function-structure decorrelation) (1). Here we compared the brain function-structure relationship during the awake state and three different anesthetics (ketamine, sevoflurane, propofol) in non-human primates and extracted a general cortical brain signature of anesthesia. We scanned five rhesus macaques at a 3T scanner at rest while they were awake or anesthetized with either propofol, ketamine, or sevoflurane, that suppress consciousness through distinct molecular mechanisms. Simultaneous EEG recording ensured for a consistent level of anesthesia across animals and sessions. We applied both stationary and dynamic analysis (2) to the resting state functional MRI. Resting state data were clustered into independent brain configurations by using an unsupervised clustering method. Under ketamine, sevoflurane and propofol anesthesia, consciousness is suppressed, while the brain still exhibits rich functional correlations patterns. The awake resting-state is characterized by a high degree of temporal flexibility with a greater variety of brain states (low function-structure correlation). All tested anesthetics reduced the repertoire of functional brain configurations to a small number of configurations, compared to the awake state. Moreover, the brain configurations that dominate during anesthesia, closely match the anatomical connectivity of the primate brain (high function-structure correlation). Whatever the molecular agent, anesthesia led to the same profile of resting-state reconfiguration of functional brain states, showing that the remaining connectivity patterns become strongly related to the underlying anatomical structure. Anesthesia is consistently characterized by a striking loss of functional correlations within a global workspace network that includes prefrontal, parietal and cingulate cortices, thus giving rise to a recognizable cortical signature of anesthesia-induced loss of consciousness.

References: 1. Barttfeld et al PNAS 2015 2. Allen et al Cereb Cortex 2014

Disclosures: L. Uhrig: None. J. Sitt: None. A. Jacob: None. J. Tasserie: None. P. Barttfeld: None. M. Dupont: None. S. Dehaene: None. B. Jarraya: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

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Program #/Poster #: 081.05/EEE10

Topic: H.01. Animal Cognition and Behavior

Support: MH081843

MH098631

Title: Frontostriatal circuit, receptor and neural coding mechanisms underlying the cognition-improving vs. cognition-impairing actions of psychostimulants

Authors: *R. C. SPENCER, C. W. BERRIDGE
Univ. of Wisconsin, Madison, WI

Abstract: The prefrontal cortex (PFC) and extended frontostriatal circuitry play a critical role in higher cognitive function. Dysregulation of frontostriatal-dependent cognition is implicated in a variety of behavioral pathologies including addiction and ADHD. Psychostimulants are well known to exert dose-dependent cognitive actions. Specifically, at higher doses associated with psychostimulant abuse, these drugs robustly impair frontostriatal-dependent cognition. In contrast, low-doses used in the treatment of ADHD, improve PFC-dependent cognitive function. Currently, our understanding of the neurocircuitry and neural coding bases for these diverse cognitive actions of psychostimulants are unclear. To address this, we infused various doses of MPH methylphenidate (Ritalin) into distinct nodes of the frontostriatal network. These studies revealed that MPH acts within the dmPFC to improve, but not impair working memory. Additional studies examined the MPH actions on task-related spiking activity of neurons in the dorsomedial PFC (dmPFC) and dorsomedial striatal (dmSTR) as well as changes in the power spectral density within these regions as measured with local field potentials (LFP). Cognition-impairing doses of MPH robustly suppressed the activity of dmPFC neurons strongly tuned to delay and reward, while activating neurons not tuned to correct tone. In contrast, in the dmSTR, cognition impairing doses of MPH had no effect on neurons strongly tuned to task events, while increasing firing of neurons not strongly tuned to these events. Interestingly, cognition-improving doses had a minimal impact on task-related firing of either PFC or striatal neurons. In terms of LFP spectral density during the delay, MPH elicited a dose-dependent decrease in low theta (3-7 Hz) power in the PFC, but not the dmSTR. Cognition-impairing doses robustly increased high theta (7-12 Hz) and gamma (40-80 Hz) LFP oscillations in the PFC and dmSTR. These observations indicate that the cognition-improving vs. cognition-impairing effects of psychostimulants target different aspects of neuronal coding.

Disclosures: R.C. Spencer: None. **C.W. Berridge:** None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

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Program #/Poster #: 081.06/EEE11

Topic: H.01. Animal Cognition and Behavior

Support: NSF EPSCOR 1632738

NIH NIGMS R25 GM083270

Carney Institute for Brain Science Innovation Award

Title: Prefrontal cortex dynamics during sequential tasks using awake behaving nonhuman primate fMRI

Authors: *N. YUSIF RODRIGUEZ¹, T. M. DESROCHERS^{1,2,3}

¹Neurosci., ²Dept. of Psychiatry and Human Behavior, ³Carney Inst. for Brain Sci., Brown Univ., Providence, RI

Abstract: Tasks like giving a presentation can be considered abstract or non-motor sequences that demand internal monitoring (keeping track of slides), to complete a final goal (complete presentation). Despite the pervasiveness of abstract sequential tasks, little is known about their cognitive and neural mechanisms. Recent work showed that increasing (“ramping”) activation in the rostralateral prefrontal cortex (RLPFC) is necessary for abstract sequential tracking in humans (Desrochers, et al., 2015). It is unknown if similar dynamics and brain areas govern sequence monitoring in monkeys. We tested this question using functional magnetic resonance imaging (fMRI) in monkeys as they fixated while passively viewing sequential visual stimuli. Monkeys were habituated to sequences of stimuli, then exposed to deviations from the established sequence either in number or in pattern (based on Wang, et al. 2015). Preliminary data show responses to sequence deviants in the prefrontal cortex (PFC) and an associated network of areas similar to previous studies performed with auditory stimuli. Further, we observed ramping activation in the PFC much like previous findings in humans. These results suggest similarities in PFC dynamics between monkeys and humans during sequence monitoring, enabling future cross-species comparisons.

Disclosures: N. Yusif Rodriguez: None. T.M. Desrochers: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.07/EEE12

Topic: H.01. Animal Cognition and Behavior

Support: VA CDA
BWF CAMS
NARSAD

Title: Measuring large-scale network activity during cognitive control in rodents

Authors: *N. BUSCHER^{1,3}, A. OJEDA^{2,1}, T. TANG¹, C. CHANG¹, S. HULYALKAR¹, J. MISHRA¹, D. RAMANATHAN^{1,3}

¹Dept. of Psychiatry, ²Dept. of Electrical & Computer Engin., UC San Diego, La Jolla, CA;

³Mental Hlth. Services, VA San Diego Healthcare Syst., La Jolla, CA

Abstract: Cognitive control is an assembly of crucial functions that underlie the ability to interact with an ever-changing environment. These key abilities enable an individual to

accomplish goal-directed tasks while ignoring irrelevant stimuli (distractor suppression), suppressing prepotent responses (response inhibition), and maintaining items in working memory. Moreover, subjects must be able to learn and adapt their behavior flexibly, requiring intact processing of reward contingencies. Such functions have been studied extensively in humans, using tasks including flanker tasks to study processing of irrelevant distractors; go/no-go tasks to study response inhibition; and various types of reward-related tasks with changing/random contingencies. However, developing a detailed and causal understanding of brain networks involved in these cognitive tasks requires testing in non-human animals. Here, we describe the development of an open-source experimental environment that allows translation of these common cognitive paradigms from humans to rodents. In these studies, we combined multi-site local field potential recordings with a novel battery of translational behavioral read-outs, assessed in an in-house designed operant and touchscreen-based testing environment. LFP and single unit recordings in several cohorts of rats were coupled with video recordings while the animals performed behavioral readouts for attention, behavioral flexibility, response inhibition, and distractor control. The open-source behavioral chamber we developed for this purpose uses a RaspberryPi to read IR sensors and control reward motors; with a MATLAB Simulink-based controller. Using this set-up, we will describe the neural activity and “functional connectivity” from multiple brain areas, including the prefrontal cortex, hippocampus, striatum, thalamus and nucleus accumbens associated with these cognitive tasks. In addition, we will explore how brain networks observed in rats compared with classic cognitive-control, attentional, working-memory and default-mode networks observed in humans. The platform developed consisting of this combination of multi-site electrophysiological readouts with behavioral paradigms translated from the clinic and executed in the operant touchscreen box will allow for unique insights into network activity underlying the described cognitive operations required to complete the behavioral challenges. Ultimately, we hope this will lead to a better grasp of the neurobiological basis of cognitive control and the development of improved disease models and technology to help those struggling with psychiatric disorders.

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Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

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Program #/Poster #: 081.08/EEE13

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH112746

Title: Testing burst coding models of working memory with spike trains from primate prefrontal cortex

Authors: *D. LI¹, C. CONSTANTINIDIS³, J. D. MURRAY²

²Dept. of Psychiatry, ¹Yale Univ., New Haven, CT; ³Wake Forest Univ. Sch. of Med., Winston Salem, NC

Abstract: Working memory (WM) requires the brain's ability to convert a brief stimulus-driven signal into an internal representation that can then be maintained across a mnemonic delay of several seconds. In prefrontal cortex (PFC), a neuronal correlate of WM is stimulus-selective persistent activity during the delay. This hallmark persistent activity is typically measured by the elevated mean firing rate, averaged across trials for a stimulus condition, and therefore may obscure more complex patterns of spiking on individual trials. It was recently proposed that observed persistent activity in WM may be an artifact of trial averaging, and that WM is instead subserved by sparse intermittent bursts of neural activity (Lundqvist et al., Neuron 2016). However, the predictions of this alternative burst-coding WM proposal for single neuron spiking activity have not been characterized or tested.

To investigate this debated issue, we applied the theory of stochastic processes and analysis of single-neuron recordings from PFC during WM tasks, focusing on measures of across-trial variability such as Fano factor (FF). We first mathematically formalized the burst-coding proposal through a doubly-stochastic inhomogeneous Poisson process model, in which the underlying firing rate transitions follow a two-level telegraph process. This model admits an analytical expression for the FF. We demonstrated analytically and numerically that under the burst-coding model, as opposed to the persistent-activity model, elevated WM activity should exhibit an increase in FF. These conclusions are robust under the introduction of refractoriness. Based on these properties of our model, we tested the plausibility of the burst coding mechanism by analyzing activity of many single neurons in monkey PFC during two classic WM tasks used in primate electrophysiology: the oculomotor delayed response task and the vibrotactile delayed discrimination task. We found that among neurons with selective mean WM delay activity, the majority of cells do not exhibit the variability signatures predicted by the burst-coding model, although a small number do exhibit some burstiness. We also found that globally there tends to be a reduction in FF during the stimulus presentation and WM delay relative to the foreperiod, consistent with prior studies and inconsistent with predictions from the burst-coding model. These results suggest that for these WM tasks, single-neuron spiking activity does not exhibit hallmarks of WM coding by sparse intermittent bursting. Our mathematical and computational framework can be further used to characterize candidate models of WM representations.

Disclosures: D. Li: None. C. Constantinidis: None. J.D. Murray: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

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Program #/Poster #: 081.09/EEE14

Topic: H.01. Animal Cognition and Behavior

Support: Simons Foundation Postdoctoral Fellowship
NIH grant R01MH108358

Title: Representations and causal contributions of frontal cortical regions during a flexible decision-making task

Authors: *M. PAGAN¹, C. D. BRODY²

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Abstract: Our ability to flexibly select, based on context, the relevant information to form decisions is a fundamental cognitive process, yet its underlying neural mechanisms are still not well understood. To address this issue, we have trained rats to perform a task requiring context-dependent selection and integration of sensory information (adapted from Mante et al., Nature, 2013). As we described in Pagan et al., SFN, 2016, on each trial of the task rats are presented with a train of auditory pulses, where each pulse can either be high-frequency or low-frequency, and each pulse is either played by a speaker to the left or a speaker to the right of the rat. In blocks of “location trials” rats are rewarded if they orient toward the side where the largest number of pulses was played (thus ignoring the frequency of the pulses). In blocks of “frequency trials” rats are rewarded for orienting right if the total number of high-frequency pulses was greater than the total number of low-frequency pulses, and for orienting left if the total number of low-frequency pulses was greater than the total number of high-frequency pulses (thus ignoring the location of the pulses). Therefore on each trial the rat is required to select the relevant feature depending on the task context. Here we present data obtained from electrophysiology and optogenetics experiments targeted at frontal cortical regions while the rats performed the task.

Disclosures: M. Pagan: None. C.D. Brody: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

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Program #/Poster #: 081.10/EEE15

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Senior Fellowship 202810/Z/16/Z

Title: Neural and ensemble underpinnings of medial prefrontal cortical population dynamics during flexible decision making and sleep

Authors: A. P. F. DOMANSKI¹, N. P. WHITELEY², *M. W. JONES³

¹Physiology, Pharmacol. & Neurosci., ²Sch. of Mathematics, ³Univ. of Bristol, Bristol, United Kingdom

Abstract: The medial prefrontal cortex (mPFC) is critically involved in executive functions such as flexible decision-making. Rodent mPFC can be anatomically subdivided into cingulate (ACC), pre- (PrL) and infra-limbic (IL) cortex, yet the nature of information flow between these subdivisions during cognition and sleep remains poorly defined. We addressed this using chronic extracellular recordings from the mPFC of adult rats implanted with Neuropixel probes[1], permitting simultaneous capture of spikes and local field potential (LFP) activity from hundreds of neurons spanning the axis of ACC/PrL/IL cortices. Following implantation, rats were trained over 14 days to navigate a 3-armed maze using a cyclic alternation rule for sucrose reward. We quantified the encoding of behavioral variables by task context-dependent firing rates of individual neurons, and identified cell ensembles as stereotyped spike patterns at 5-500ms resolution[2] between neurons separated by up to 5mm of tissue. The firing rate modulation of mPFC single neurons provided rich information about start and end locations of the animals' runs, the readout of which peaked at choice points consistent with a role of these neurons in decision making. We did not find any evidence for anatomical organization of the encoding of task variables between ACC/IL/PrL neurons. Cell ensemble activities, organized by phase of the LFP theta (5-10Hz) and gamma (30-80Hz) cycles, were observed between ~20% of potential pairwise unit interactions. Compared to constituent single units, assembly activation patterns provided stronger readout of behavioral variables. Multi-neuron spike patterns of cell ensembles could link neurons with disjoint rate-encoded variables to represent different task-related information, thereby supporting a multiplexed spike rate-time code. During post-task sleep, mPFC spindle (12-18Hz) oscillations were observed in the LFP as discrete local (0.2-500 μ m) or global (>4500 μ m) events. To analyse the extent to which these spindle categories differentially affected local and long-range network dynamics, we developed a Markov process model of ensemble firing activity which allows a state-space trajectory summarizing time-varying couplings between neural pools to be inferred from data, and can be fitted efficiently using

parallel algorithms. This work demonstrates both integration and segregation of functional information processing in the mPFC and provides novel insights into the logic of network computations supporting reasoning in cognitive tasks and reorganization during sleep. [1] Jun, Steinmetz et al. Nature 2017; [2] Russo & Durstewitz eLife 2016

Disclosures: A.P.F. Domanski: None. N.P. Whiteley: None. M.W. Jones: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

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Program #/Poster #: 081.11/EEE16

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R37MH087027

The MIT Picower Institute Innovation Fund
ONR MURI N00014-16-1-2832

Title: Beta-Gamma rhythms control the balance between cognitive flexibility and predictability

Authors: *A. BASTOS, M. LUNDQVIST, E. K. MILLER

The Picower Inst. for Learning and Memory and Dept. of Brain and Cognit, MIT, Cambridge, MA

Abstract: Cognitive flexibility refers to the continual updating of rules, sensory-motor mappings, working memory, etc as a function of changing demands. It is dependent on prefrontal cortex (PFC). Cognitive predictability, by contrast, refers to exploiting environmental regularities to maximize performance. To study their neural basis, we trained two monkeys on a delayed match to sample task (DMS). Monkeys were cued with a sample stimulus which had to be held over a short delay. Over blocks of 50 trials, the sample stimulus could either be drawn randomly or held constant. Thus, monkeys switched between performing based on a constantly switching sample (cognitive flexibility) or repeats of the same sample (cognitive predictability). Reaction times were faster and accuracy was better for predictable vs switching samples. We recorded neuronal activity in visual (V4), parietal (LIP/7A), and prefrontal (FEF/DLPFC/VLPFC) using multilaminar probes to record spiking and local field potentials across cortical layers. During cognitive flexibility these areas showed stronger gamma-band (50-150 Hz) power and enhanced spiking during sample processing, consistent with greater demand on working memory updating. During cognitive predictability, beta-band (15-30 Hz) power was stronger and spiking was weaker, again especially in PFC. Across all areas, gamma rhythms predominated in superficial layers (layer 2/3) and beta in deep layers (layer 5/6). Thus, the relative balance between beta and gamma might switch cortical processing from relying on deep layer predictions based on statistical regularities (via beta) to relying on more superficial layer

bottom-up cue information (via gamma) to continually update working memory and thus endow flexibility.

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Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

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Program #/Poster #: 081.12/EEE17

Topic: H.01. Animal Cognition and Behavior

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Title: Modeling of oscillatory gating for cognitive function

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Abstract: Adaptive cognition requires dynamic mechanisms that can flexibly gate and route signals in different ways using the same underlying neural circuitry. Changes in oscillatory synchronization across rate-coding populations of neurons in prefrontal cortex (PFC) have been implicated in a variety of cognitive tasks that require flexible routing. In this work, we used biophysically detailed, computational modeling to explore how PFC oscillations can gate the flow of rate-coded signals for cognitive function. First, we modeled the deep layer as an output gate for a working memory (WM) buffer in the superficial layers of PFC. Using a version of our model that includes multiple WM items represented by rate-coding populations in different dynamical regimes (asynchronous activity and periodic activity with variable synchrony and frequency), we show that the dynamical states of input populations can exhibit a stronger influence over downstream competition in the output layer than the activity levels (firing rates) of the inputs. Specifically, when multiple inputs from parallel (or convergent) pathways drive target populations connected to shared interneurons, these dynamics bias competition in favor of the most population frequency-resonant input (i.e., the input producing an output oscillation closest to the peak frequency that can be generated by the output gate). Essentially, the output population with the shortest period between volleys of output spikes tends to be the dominant driver of local inhibition that suppresses all populations connected to the same interneurons.

Furthermore, this form of biased competition, mediated by oscillations, can be amplified to produce winner-take-all selection (gating) by plasticity of recurrent connections that strengthen output responses (e.g., across repeated trials of task). The result is an output gate governed by the correspondence between its resonant frequency and the input population frequency of oscillatory items in the WM buffer. Finally, by adding rule-selectivity to interneurons in the superficial layer, we demonstrate how context-dependent input-output mappings can be selected using this dynamic mechanism, enabling flexible action control to be mediated by PFC oscillations instead of firing rates. Our model predicts that the experimentally-observed PFC beta and gamma oscillations could leverage population frequency-resonance to bias responses in the output layer, and that task-related modulation of oscillatory synchronization could govern the flexible routing of signals in service of cognitive processes like output gating from a working memory buffer and the selection of rule-based actions.

Disclosures: J. Sherfey: None. S. Ardid: None. J. Hass: None. N.J. Kopell: None. E.K. Miller: None. M.E. Hasselmo: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: R01-MH55806

P30-EY08126

Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience

Title: Microcircuitry of performance monitoring: Laminar structure of visual and conflict monitoring in the supplementary eye field

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Abstract: We are continuing our investigation of the microcircuitry of supplementary eye field (SEF), an agranular area supporting encoding of visual stimuli and response conflict. Previous work has described neurons encoding visual cues, reward prediction, and response conflict (Stuphorn et al. 2000). However, the laminar distribution of these signals is unknown. With linear electrode arrays, we sampled neural spiking across all layers of SEF while recording overlying EEG in two monkeys performing the saccade countermanding (stop-signal) task. In this task, monkeys earned fluid reward a constant interval after a secondary tone reinforcement for shifting gaze to a peripheral visual target unless a fixation stop signal appeared. The location of the target cued that either a large or small magnitude of reward could be obtained on the

current trial. The assignment of reward magnitude alternated across blocks of ~20 trials. Systematic variation of response time demonstrated monkeys' sensitivity to the reward value. On ~50% of stop-signal trials monkeys shifted gaze in spite of the stop signal; these were followed by a distinct tone reinforcement. The probability of non-canceled errors increased with stop signal delay, and the response times (RT) of errors were consistently less than the RT on trials with no stop signal. Thus, stop signal reaction time (SSRT) could be determined from the Logan model of a race between GO and STOP processes. Response conflict occurs when the GO and STOP processes are co-active during successfully canceled stop signal trials. We isolated 293 neurons across all SEF layers. Neurons responding to the visual target were concentrated in L2, L3, and upper L5 but absent in L6. Responses were commonly more vigorous to targets associated with smaller reward. Responses also varied with RT. Neurons modulating after SSRT on canceled trials were concentrated in L2, L3, and L5. Overall, neurons with wide spikes were distributed across layers, but those with narrow spikes were concentrated superficially. These findings offer new details and insights to inform the first draft of a cortical microcircuit that enables agranular cortex to exert proactive inhibition in response to the conditions and consequences of performance

Disclosures: S.P. Errington: None. A. Sajad: None. J.D. Schall: None.

Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.14/EEE19

Topic: H.01. Animal Cognition and Behavior

Support: UNLV FOA
CIHR

Title: Living in the moment: How ACC ensembles accurately reflect the current reality rather than the recent past

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Abstract: A central assumption of the Rescorla & Wagner (RW) model, and all models based upon it such as temporal difference learning, is that learning is preserved until new, contradictory information is encountered. Neurons that appear to follow this rule and display stronger responses to cues/actions previously paired with reward have been found from the brainstem to the cortex, but how these signals manifest across neuronal ensembles is not clear. Here we tested whether these models could also be applied to the ensembles of anterior cingulate cortex (ACC) neurons. Rats were trained on a differential reward probability task where they were cued to

nose-poke at 1 of 3 ports that delivered reward at a high (75%), medium (50%), or low (25%) probability, where the high and low probability ports reversed halfway through each session. Importantly, the probabilities on each session started out the same as they ended the previous session and behavioral measures confirmed that preferences for the high-reward option remained intact. We captured new ACC ensembles each session and ran a principal component analysis (PCA) on their activity across the ensemble during the nose-pokes. We then correlated PC scores to RW reward predictions per trial under 2 conditions. In the retention condition, the RW reward predictions for the 3 options at the start of a session were set to be the same as on the final trials from the prior session (i.e. .75, .50, .25), whereas in the no-retention condition the predictions of the 3 options at the start of a session were all set to 0. Since PCA orthogonalizes signals by the proportion of neuronal variance they account for, we assessed model fit across these proportions for both conditions. We reasoned that if RW learning rules were robustly represented in ACC activity, then there should be a positive correlation between degree of model fit and percent variance accounted for across PCs. The retention RW model fit ACC ensemble data from the whole session ($R=.512$), and tracked the changes in the PCs that occurred even at the reversals. Surprisingly, the no-retention RW model fit with even higher affinity ($R=.602$). This effect was even more striking for the pre-reversal trials (retention condition, $R=.009$; no-retention condition, $R=.317$), where the limited number of trials made the lack of retention even more pronounced. These results suggest that the dominant patterns of activity in ACC ensembles can be explained using RW-like learning rules within a session, but not across sessions. Notably, despite the fact that the animal retained information across sessions, ACC ensembles appeared to start each session with a blank slate onto which they can learn about the current reality.

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Poster

081. Animal Cognition and Behavior: Executive Function: Network Activity

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 081.15/EEE20

Topic: H.01. Animal Cognition and Behavior

Title: Hyperglycemia induces altered hippocampal and anterior cingulate cortex oscillations

Authors: *R. A. WIRT, A. A. ORTIZ, N. L. KAPLAN, D. GOROKHOVSKAYA, S. HERNANADEZ, L. A. CREW, J. W. KINNEY, J. M. HYMAN
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Abstract: Alzheimer's disease (AD) is a debilitating neurodegenerative disorder known to cause progressive cognitive and memory impairments. Despite considerable progress elucidation of the cause and the development of effective treatments are needed. Several risk factors have been

identified, including diabetes mellitus (DM). DM is associated with altered insulin signaling as well as elevated blood glucose levels, or hyperglycemia. We have previously demonstrated that sustained hyperglycemia in an otherwise healthy animal induces learning and memory impairments, elevated ptau, and neuroinflammation, suggesting a mechanism to increased risk for AD. In this study, we examined how neural network activity was altered as a result of prolonged hyperglycemia. We trained subjects on a T-Maze delayed alternation, a spatial working memory task previously shown to rely on interactions between the hippocampus (HC) and anterior cingulate cortex (ACC). After subjects were proficient at the task, in a group of animals we induced a lasting hyperglycemic state via multiple low dose injections of streptozotocin, which destroys insulin producing pancreatic beta cells inducing CNI and memory impairments. We simultaneously recorded local fields potentials from the ACC and HC while both control and hyperglycemic animals performed the task. We found that hyperglycemic animals performed significantly worse on both short and long delay trials, indicating substantial impairments in spatial working memory. Next, we compared differences in theta (5-12 Hz) and delta band (1 – 3 Hz) oscillations. Electrophysiological data revealed that subjects in the hyperglycemic state had altered neural oscillatory activity, such that, theta power in the HC and ACC was increased and delta power in both areas was decreased. We also found significant disruptions in theta coherence between the HC and ACC. Our data indicate that the same hyperglycemic state that is associated with increased ptau and inflammation in the brain results in altered oscillatory activity consistent with genetic mouse models of AD.

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Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.01/EEE21

Topic: H.01. Animal Cognition and Behavior

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CFI Leaders Opportunity Fund 25026
CIHR Operating GrantMOP-133693

Title: Lateral entorhinal cortex selectively routes mnemonic features of stimuli to the medial prefrontal cortex

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¹Cell And Systems Biol., ²Cell & Systems Biol., ⁴Dept. of Psychology, ³Univ. of Toronto, Toronto, ON, Canada

Abstract: The ability to form associations between temporally discontinuous stimuli is dependent on an inter-connected network that consists of many forebrain regions, including the medial prefrontal cortex (mPFC) and the lateral entorhinal cortex (LEC). Previously we have shown that as rats associate a neutral stimulus with a mild eyelid shock in trace eyeblink conditioning (TEBC), the mPFC and LEC became synchronized at theta band oscillations (4-12 Hz) during the interval between the stimulus and shock (Takehara-Nishiuchi et al., 2012). This, along with monosynaptic connections between these regions (Kerr et al., 2007), suggests close interactions between the mPFC and LEC during temporal associative learning. It remains unknown, however, exactly what type of information is transferred from the LEC to the mPFC during learning. To address this point, we reversibly inactivated the LEC via microinfusions of the GABAA receptor agonist muscimol, whilst recording local field potentials within the mPFC as rats underwent a differential TEBC task. Daily conditioning involved intermixed presentations of 50 trials in which a tone was paired with a mild eyelid shock that occurred after a stimulus free trace interval, and 50 trials in which a light flash was presented alone. Task learning was measured by calculating the percentage of trials in which rats expressed an anticipatory eyeblink response (CR%) following presentations of either tone or light. Compared to controls, LEC inactivated rats showed a significantly lower asymptote of CR% to the reinforced tone stimulus after 10 days of conditioning, whilst CR% to the unreinforced light stimulus was comparable between the groups. During the early days of conditioning, wherein both inactivated and control rats showed similar CR%, the amplitude of stimulus-evoked theta band activity was comparable between LEC inactivated and control rats. However, as control rats started showing increased CR% to the reinforced tone stimuli, their evoked theta activity in response to presentations of both reinforced tone and unreinforced light stimuli became stronger than LEC inactivated rats. These findings suggest that the LEC comes to modulate stimulus-evoked theta band activity in the mPFC as rats learn to selectively associate punishment to one of the stimuli. The experience-dependent modulation that the LEC exerts on the mPFC network activity counters the traditional view whereby the LEC serves as a passive relay of stimulus information. Rather, the LEC selectively routes to the mPFC the conjunctive information of stimuli and their history associated with a given environment.

Disclosures: X. Yu: None. J. Jarovi: None. K. Takehara-Nishiuchi: None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.02/EEE22

Topic: H.01. Animal Cognition and Behavior

Support: ONR MURI N00014-16-1-2832

NIMH R37MH087027

Title: Neural population dynamics in prefrontal cortex and hippocampus during learning of associations

Authors: *Y. LIU^{1,2}, S. L. BRINCAT³, E. K. MILLER³, M. E. HASSELMO¹

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Abstract: Recently there has been work studying the change of population dynamics during motor learning. Here we aim to utilize similar techniques to characterize population level changes in neural activity in hippocampus and prefrontal cortex (PFC) as monkeys learn to perform a paired associate task (Brincat and Miller, 2015, 2016). It was found that the overall neural activity changes with learning for hippocampus, but not PFC. The stability of the population code as measured by the angular speed of the neural trajectories also shows differences between PFC and hippocampus. This indicates differences between PFC and hippocampus in the dynamics of local circuits.

Furthermore, a reduction of population firing rate variability was found following any stimulus onset. This phenomenon was termed a “quench” of neural variability and was argued in a previous study to be a widespread cortical phenomenon (Churchland et al., 2010). Building on this, we found that the magnitudes of the quench followed by stimuli with different roles (cue versus associate) exhibit interesting changes with learning. In particular, the magnitude of the quench for the associate changes with learning in specific structures only in PFC but not in hippocampus. Previous works have related firing rate variability with task difficulty (Horwitz and Newsome, 2001) and attention level (Mitchell et al., 2007, Cohen and Maunsell, 2009). Based on this evidence, our results suggest that during learning, the PFC network shifts from being driven by external stimulus to being driven by internal signals.

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Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.03/EEE23

Topic: H.01. Animal Cognition and Behavior

Support: JSPS Grant 16H07444
JSPS DC 14j02824

Title: Hippocampal-retrosplenial-prefrontal circuit dynamics in nonspatial associative memory in rats

Authors: *S. TERADA^{1,2}, S. FUJISAWA²

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Abstract: Although the interaction of the hippocampus and prefrontal cortex (PFC) is thought to play a key role in associative memory, the anatomical connection between these structures is relatively sparse. The retrosplenial cortex (RSC), the posterior part of cingulate cortex, has dense connections with both CA1 and PFC, thus it is hypothesized to support information transfer between them. However, little is known about how RSC interact with CA1 and PFC in information processing related to associative memory. Here, we investigated task-related neuronal activity in PFC, RSC, and CA1 during the cue-combination task, which requires the rat to associate odor and sound cues for making a correct choice. A prominent increase of theta coherence between CA1 and RSC was observed during task trials. PFC gamma power was also correlated with the theta oscillations. Subsets of both RSC and PFC neurons were significantly phase-modulated by the theta oscillations. Cross-correlation analysis revealed that a large number of pairs of RSC and hippocampal neurons showed synchronous firing activity in the timescale of single theta cycles. These results suggest that theta oscillation could support information processing across CA1, RSC, and PFC.

Disclosures: S. Terada: None. S. Fujisawa: None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.04/EEE24

Topic: H.01. Animal Cognition and Behavior

Support: R01MH106552
R01MH112523

Title: Role of hippocampal place cells and neurons in the anterior cingulate cortex in social learning of a reward-guided navigation task

Authors: *X. MOU¹, E. PATEL², P. SURESH³, D. JI¹

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Abstract: Social animals frequently acquire new knowledge and learn new skills from observing other animals' actions. How neural circuits in the brain enable animals to learn by social

observation is unknown. Here we test a hypothesis that hippocampal place cells and neurons in the anterior cingulate cortex (ACC) mediate the social learning of a spatial navigation task in rats. We designed a novel reward-guided social learning task that required synchronized nose-poking behavior of two rats: The observer rat in a box learned to poke spouts shortly after a demonstrator rat poking on a nearby T-maze for water reward. More importantly, the observer rat learned to retain the demonstrator's choice on the T-maze and make the corresponding decision on the same maze after 20~30 second delay on a trial-to-trial basis. We recorded hippocampal place cells and ACC cells from the observer rat in the task. We observed that some place cells in the observer also respond to demonstrator's behavior. About 35% place cells representing the T-maze central arm displayed distinct firing rates when the observer rat made left vs. right choice. Moreover, the majority of ACC cells showed high firing rates before the animal set out, at the choice point, and/or approaching the reward sites on the T-maze. Those ACC cells often became active when the demonstrator was at one or more of the three locations too. Therefore, our social learning task allows us to examine specific roles of hippocampal place cells and ACC neurons in social learning of spatial navigation. Our data suggest that ACC neurons mediate social transfer of spatial information encoded by hippocampal place cells between animals. The finding may contribute to the neural mechanism of social learning.

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Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

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Program #/Poster #: 082.05/EEE25

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH0995902

Title: Diverse electrophysiological firing properties of ventral midline thalamic cells across the sleep-wake cycle of the rat

Authors: *T. D. VIENA¹, S. B. LINLEY², R. P. VERTES³

¹Ctr. for Complex Systems and Brain Sci., ²Florida Atlantic Univ., Boca Raton, FL; ³FAU/Ctr Complex Systems, Boca Raton, FL

Abstract: Previous research has clearly established the role of the reuniens (RE) and rhomboid (RH) nuclei of the ventral midline thalamus (VMT) in higher order cognitive functions such as working memory and goal directed behaviors (Layfield et al. 2015; Linley et al., 2016; Ito et al., 2015; Viena et al., 2018). The VMT is strongly reciprocally connected with the hippocampus and medial prefrontal cortex (mPFC). In addition, the VMT is associated with the 'nonspecific

arousal' system due to its diverse inputs from the brainstem reticular formation and relatively diffuse projections to the cerebral cortex (Vertes et al., 2015). However, little is known about the electrophysiological discharge properties of VMT cells across the sleep-wake cycle in the behaving rat. Here, we examined the discharge properties of VMT cells across wake (W), slow wave sleep (SWS) and REM sleep (REM) by recording extracellularly in freely moving rats. A drivable microelectrode was implanted targeted for the VMT to record single unit activity. Wake/sleep states were identified by recording neck muscle EMG activity, hippocampal and cortical EEG activity and visual observation (video recordings) of behavior. Following a period of sleep deprivation (SD; 6-12 hours), rats were placed in a recording chamber and allowed to forage for food for 5 minutes. After this active period, rats were permitted to sleep naturally while units (and other measures) were recorded (2-4 hours). We identified negative-positive spikes (N-P), solely negative spikes (N) and almost symmetrical positive-negative spikes (P-N). In general, all VMT neurons decreased firing during SWS compared to W and REM. N-P, N and P-N cells exhibited different rates of activity across sleep/wake states ($p < 0.01$). Mean firing rates of each of these classes of cells was significantly higher in W and REM than in SWS ($p < 0.05$), but not significantly different across W and REM states. During SWS sleep, some units fired rhythmically in bursts, while others were associated with rhythmical cortical slow (delta) wave activity. The diversity in the neuronal firing patterns of VMT cells across sleep/wake states is consistent with their varied input from the brainstem, diencephalon, basal forebrain and cortex (McKenna and Vertes, 2004) which likely contributes to their direct involvement in vigilance states (Van der Werf et al., 2002). In summary, our results support the idea that the ventral midline thalamus (RE/RH) is involved in arousal/attention related states.

Disclosures: T.D. Viena: None. S.B. Linley: None. R.P. Vertes: None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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NSERC CREATE Grant to LK

Title: Memory-trace replay in rat medial prefrontal cortex occurs in a substate of cortical UP state during slow wave sleep

Authors: L. KALVI^{1,2}, A. PONCE-ALVAREZ³, S. MALEK¹, K. ALI¹, D. R. EUSTON¹, S. GRUEN^{4,5}, *M. TATSUNO¹

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Abstract: Memory-trace replay of declarative memory has been predominantly observed during sharp-wave ripples (SPWRs) in the hippocampus and during UP states in the neocortex. Their interaction is conjectured to play an important role in transferring memory from the hippocampus to the neocortex. Recent evidence suggests that SPWRs can be clustered into subtypes (Ramirez-Villegas et al., 2015). However, it is not clear if there are subtypes/substates of UP states in the neocortex. We analyzed multi-neuronal spiking activity in rat medial prefrontal cortex. Three rats were trained to run a sequential task on a circular arena (Euston et al., 2007). The data typically consisted of 30-min pre-rest, 1-hour behavior training, and 30-min post-rest periods and the analysis was composed of four steps. First, the epochs of UP-DOWN oscillations within motionless periods were assessed by large fluctuations of smoothed multi-unit activity. Second, UP and DOWN states were separated by a hidden Markov model (HMM). Percent of spikes and the mean firing rate in the detected UP (DOWN) states were 93.7% (6.27%) and 2.52 Hz (0.23 Hz), respectively. Third, in order to detect UP ‘substates’, the UP states were concatenated and a HMM was applied again. By changing the number of hidden states in the HMM, different sets of UP substates were obtained. Fourth, the separation of UP substates was assessed by principal component analysis (PCA) as well as t-distributed stochastic neighbor embedding (t-SNE) which is a machine learning technique for nonlinear dimensionality reduction. We found that UP substates were often grouped into two distinct clusters even if more substates were found in the analysis step 3. These two UP substates have different distributions of duration and firing rate. Most interestingly, we found that memory-trace replay predominantly occurred in one type of substate that is characterized by fast decorrelation of similarity between neighboring population vectors of firing rate with the bin width of ~15 msec. Taken together, the results suggest that a cortical UP state is not a single and stationary state but rather it consists of at least two substates that may be organized dynamically. We speculate that the UP substates with fast population-vector decorrelation consolidate recent experiences while UP substates with slow decorrelation process other information. This view is consistent with the finding that memory-trace replay of recent experience in rat medial prefrontal cortex is temporally compressed by 4-8 times (Euston et al., 2007) because compressed replay implies the fast change of the brain states that can be measured by fast population vector decorrelation.

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Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.07/FFF1

Topic: H.01. Animal Cognition and Behavior

Title: Task-related oscillatory interactions within the midline thalamic-hippocampal-prefrontal network

Authors: *H. MEI, N. LOGOTHETIS, O. ESCHENKO

Max Planck Inst. for Biol. Cybernetics, Tuebingen, Germany

Abstract: We have recently reported that inactivation of the midline thalamic nucleus reuniens (RE) dramatically impaired the rat performance of a previously learnt spatial task (Mei et al., 2018). Our findings supported an emerging view that the RE may contribute to spatial memory by coordinating interactions between the hippocampus (HPC) and the prefrontal cortex (PFC). The HPC-PFC interactions occurring at different frequency ranges (e.g. theta, beta, or gamma) are thought to support specific steps of information processing. However, the detailed mechanisms of task-specific cross-regional interactions within the RE-HPC-PFC network remain poorly understood. We recorded extracellular activity from the RE, dorsal HPC and medial PFC in the rats learning a complex spatial task on a cross-word maze over 5 training sessions. We aim at characterizing the learning-induced dynamics of cross regional interactions. During task performance, the strongest theta power was present in the HPC, while it was much weaker in the RE and PFC. In the beginning of each trial, we observed systematic surge of the theta-synchronization between the PFC and RE, which was followed by increases in the RE-HPC and HPC-PFC theta-coherence. This activity dynamics seemed to be associated with a retrieval of the correct trajectory at the beginning of the trial. Thus, a decision making (e.g. right or left turn) on the maze likely required retrieval of cortically-stored information and its integration into active network. A strong theta-coherence within the entire RE-HPC-PFC network accompanied errors (e.g. entries to the wrong maze alleys). Besides, we compared the coherence between the RE, HPC, and PFC across training days. Our preliminary results further support the idea that the RE may indeed gate the bidirectional information flow within the HPC-PFC pathway. The RE may contribute to spatial learning as a network element enabling retrieval and storing task-related information in working memory. It remains, however, unclear if the RE is required for consolidation of spatial memory.

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Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

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Program #/Poster #: 082.08/FFF2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH0995902

Title: Chemogenetic inactivation of nucleus reuniens impairs behavioral flexibility in an odor texture attentional set shifting task

Authors: *S. B. LINLEY¹, A. K. P. ROJAS², M. E. GORORA², M. E. SCHREIBER³, T. D. VIENA³, T. A. ALLEN⁴, R. P. VERTES⁵

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Abstract: The nucleus reuniens (RE) of the ventral midline thalamus is a major node linking the prefrontal cortex to the hippocampus. It is well established that RE plays a critical role in working memory and other mnemonic functions dependent upon the hippocampus and prefrontal cortex (Vertes et al., 2015; Griffin, 2015). However, the involvement of RE in other behaviors reliant on the hippocampal-prefrontal circuitry has not been well-studied. We recently found that inactivation of RE significantly impaired spatial working memory and behavioral flexibility on a T-maze task (Viena et al., 2018). Additionally, we showed that lesions of RE produced impairments in attention and behavioral flexibility on a set shifting task, indicating that RE plays an essential role in executive functioning (Linley et al., 2016). In the present study, we used a chemogenetic approach to examine the effects of inactivation of RE on executive behaviors using an odor texture attentional set shifting task. Long Evans rats (n=10), expressing the hM4Di DREADD in RE, were initially trained to dig in ramekins to discriminate between olfactory or tactile exemplars. Next, rats were tested in the attentional set shifting task sensitive to both the midline thalamus and the orbital and medial prefrontal cortex. Briefly, the attentional set shifting task consists of seven stages which assess attentional set, attentional set shifting, behavioral flexibility, and reversal learning using response contingencies to a particular odor or tactile exemplar. Inhibition of RE via clozapine-n-oxide (CNO, 5mg/kg), but not vehicle (saline) produced significant impairments in both rule abstractions to an attentional set and reversal learning. Furthermore, impairments in reversal learning were associated with significant perseverative responses to previously rewarded stimuli. These results confirm that RE plays a key role in goal directed behaviors. RE is not only involved in mediating mnemonic aspects of hippocampal-prefrontal connectivity but is also a core node in the modulation of executive

functions. As such, RE could be a principal target in the treatment of disorders such as schizophrenia, depression, and attention deficit hyperactivity disorder, which are characterized by impairments in hippocampal-prefrontal synchrony and mnemonic and executive dysfunctions.

Disclosures: **S.B. Linley:** None. **A.K.P. Rojas:** None. **M.E. Gorora:** None. **M.E. Schreiber:** None. **T.D. Viena:** None. **T.A. Allen:** None. **R.P. Vertes:** None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 082.09/FFF3

Topic: H.01. Animal Cognition and Behavior

Support: NIH MH0995902

Title: The effect of inactivation of the ventral hippocampus (vHF) on spatial working memory in the rat

Authors: ***M. SCHREIBER**¹, A. C. ATHANASON¹, A. K. ROJAS¹, T. D. VIENA², S. B. LINLEY¹, T. A. ALLEN³, R. P. VERTES⁴

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Abstract: It is well established that the hippocampus and medial prefrontal cortex (mPFC) are fundamental to the control of cognitive and affective behavior and dysfunction of either structure underlies several diseases including depression and schizophrenia. Electrophysiological studies have shown that ventral hippocampal (vHF) to mPFC synchrony is essential to these behaviors and disruption of this circuit produces deficits in working memory, executive functioning, and also results in anxiogenesis in the rat (Chudasama et al., 2012; Padillo-Coreano et al., 2016; Kupferschmidt and Gordon, 2018). While the vHF is positioned to directly influence the mPFC, there are no return projections from the mPFC to the vHF. The nucleus reuniens (RE) of the ventral midline thalamus is the principal return route from the mPFC to the vHF. We have previously demonstrated that inhibition of RE impairs spatial working memory (SWM) and behavioral flexibility (Viena et al., 2018). The present study examined the role of the vHF in cognition using a T-maze task. Long Evans rats were implanted with cannulas in RE and bilaterally in the vHF. Following recovery, rats were trained in a delayed (30 or 120s) nonmatch to sample (DNMS) alternation task. Rats were given no-delay correction runs, whereby they could select the correct directional response following an error. Rats received infusions of muscimol or saline into RE or vHF in separate testing sessions. Muscimol inactivation of vHF impaired SWM, while muscimol in RE impaired SWM and produced perseverative responding.

Next, we selectively inactivated RE projections to the vHF using a chemogenetic approach. In a separate group of rats, the Gi-coupled hM4D inhibitory DREADD was injected into RE and bilateral cannulas were implanted into the vHF. The selective inhibition of RE terminals to the vHF via clozapine-N-oxide (CNO) significantly impaired performance on the DNMS task compared to vehicle controls. These results indicate that the vHF plays an important role in working memory and RE acts as a critical node in the transfer of information from the mPFC to the vHF. As such, RE's pivotal role in hippocampal-prefrontal circuitry makes it a potential target in the treatment of cognitive and psychiatric disorders.

Disclosures: **M. Schreiber:** None. **A.C. Athanason:** None. **A.K. Rojas:** None. **T.D. Viena:** None. **S.B. Linley:** None. **T.A. Allen:** None. **R.P. Vertes:** None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 082.10/FFF4

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01AA021775
NIH 5U01AA01997208

Title: Chemogenetic modulation of cholinergic neurons in the nucleus basalis magnocellularis rescues acetylcholine efflux in the prefrontal cortex in rats exposed to adolescent binge ethanol exposure

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Abstract: Adolescence has been regarded as a critical window for brain plasticity such that exposure to drugs can have long-lasting deleterious effects. In rodents, adolescent intermittent ethanol (AIE) exposure reduces the number of cholinergic neurons in the nucleus basalis magnocellularis (NbM) as well as decreases activity-dependent acetylcholine (ACh) efflux in the prefrontal cortex. Utilization of designer receptors exclusively activated by designer drugs (DREADD) technology allowed us to specifically activate cholinergic neurons within the NbM. Our preliminary data indicate that binge-like AIE exposure reduces activity-dependent ACh efflux in the prefrontal cortex by 22% ($F[1,10]=7.712$, $p=0.02$), but in rats exposed to AIE, chemogenetic activation of the hM3D(Gq) receptor with compound 21 recovered activity-dependent ACh release in the prefrontal cortex ($F[1,5]=6.842$, $p=0.047$). These results demonstrate that cholinergic function in the NbM is markedly affected by AIE and that chemogenetic modulation can rescue these neurochemical deficits.

Disclosures: J.M. Hall: None. L.M. Savage: None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.11/FFF5

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grant RGPIN-2015-05458
CFI Leaders Opportunity Fund 25026

Title: Chemogenetic enhancement of prefrontal activity sharpens the selectivity of prefrontal theta oscillations for the mnemonic value of events and facilitates their encoding

Authors: *J. JAROVI¹, J. VOLLE², X. YU¹, L. GUAN², K. TAKEHARA-NISHIUCHI²
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Abstract: The ability to capture the most relevant information from everyday experiences without constantly learning unimportant details is vital to both survival and mental health. While decreased activity of the medial prefrontal cortex (mPFC) is associated with failed or inflexible encoding of relevant events in the hippocampus, the mechanisms by which the mPFC discerns the behavioural relevance of events are not clear. To address this question, we chemogenetically activated excitatory neurons in the mPFC of rats and examined its impact on local network activity as well as differential associative learning dependent on the hippocampus. The evolved human M3-muscarinic receptors (hM3Dq) were expressed in mPFC pyramidal neurons of adult rats via viral transduction. Neurons expressing hM3Dq were activated by systemic injection of clozapine-N-oxide (CNO). Rats were split into two groups, receiving either CNO or saline injections prior to daily conditioning. Rats were trained in differential trace eyeblink conditioning where they were exposed to two stimuli in two environments whose contingency with punishment changed systematically across days. During differential learning, rats were required to learn an association between one neutral conditioned stimulus (CS+) and a mild electric shock (US) while learning that the other CS- is not associated with US. In reversal learning, the previous CS+ now became CS-, and vice versa. Finally in set-shifting, both CS were paired with US in one environment, and neither were paired with US in the other environment. Over the two weeks of differential learning and subsequent reversal, stimulus-evoked theta activity came to ramp up toward the expected onset of the US and later tracked the subsequent shift of the set (stimulus modality to environment) predictive of the US. With chemogenetic mPFC activation, the ramping theta activity emerged within a few sessions of differential learning, which paralleled faster differential learning and a stronger correlation

between the ramping theta activity and task performance than in controls. Chemogenetic mPFC activation, however, did not affect the adjustment of theta activity or behavioral responses upon reversal or set-shifting, suggesting that the faster learning was not due to enhanced attention, sensory, or motor processing. Our findings suggest that the level of the mPFC network activation during sensory events provides a relevance-signaling mechanism whereby the mPFC exerts executive control over the encoding of those events in the hippocampus.

Disclosures: **J. Jarovi:** None. **J. Volle:** None. **X. Yu:** None. **L. Guan:** None. **K. Takehara-Nishiuchi:** None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 082.12/FFF6

Topic: H.01. Animal Cognition and Behavior

Support: R01AA021775

Title: Sex differences in vulnerability to alcohol-related brain damage and its functional consequences

Authors: ***B. T. KIPP**¹, L. M. SAVAGE, Ph.D.²

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Abstract: To date, sex differences in the responsiveness to chronic ethanol treatment (CET) and/or thiamine deficiency (TD) have yet to be characterized. To determine whether sex is a variable that modulates alcohol-related pathogenesis and neurobehavioral deficits, ACh efflux was measured in the prefrontal cortex and hippocampus during a spatial working memory task in rats exposed to CET, TD or combined treatment, as well as pair-fed control conditions. A set shifting task was implemented to assess cognitive flexibility, which is dependent on the prefrontal cortex. Preliminary treatment data indicates that there are no sex differences in the consumption of ethanol however, females trend toward higher blood ethanol concentrations (BECs). Attention set shifting data also suggests that CET and TD treated females display greater dysfunction on attention set shifting. To date the data suggest that although male and female rats do not differ in ethanol consumption, females display elevated BECs and prefrontal cortical impairment. Understanding sex difference in the consequences of drug and alcohol abuse are critical to developing sex-specific treatment interventions.

Disclosures: **B.T. Kipp:** None. **L.M. Savage:** None.

Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

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Program #/Poster #: 082.13/FFF7

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01AA021775

Title: Binge-type alcohol exposure during adolescence alters septohippocampal functioning as rats age

Authors: ***P. TOLEDO NUNES**¹, G. M. FERNANDEZ², J. M. HALL¹, L. M. SAVAGE¹
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Abstract: Converging data from human studies and preclinical animal models have revealed that extreme alcohol binge drinking/exposure during early adolescence is associated with changes in brain structure and connectivity. Persistent brain damage after adolescent intermittent ethanol exposure (AIE) in rodents, a model of binge drinking, entails reduced hippocampal neurogenesis (35%) and a loss of cholinergic neurons (30%) in the medial septum and diagonal band of Broca (MS/DB). The circuit formed between those regions, the septohippocampal pathway, is critical for learning and memory. We found that as rats exposed to AIE approached middle age, septohippocampal dysfunction emerged. This is in contrast to assessment in early-adulthood after AIE, in which there is normal spatial working memory (assessed by spontaneous alternation) and stable activity-dependent hippocampal acetylcholine (ACh) efflux. However, when AIE rats aged, specifically 12-months post AIE treatment, a robust spatial memory impairment was observed that was associated with blunted hippocampal ACh efflux. Our data revealed a profile of septohippocampal dysfunction that resembled alcohol-related dementia as rats exposed to AIE begin to age. Changes in the expression of forebrain cholinergic neural phenotypes and their altered connectome following AIE and aging will be explored. These results demonstrate that heavy intermittent alcohol exposure during adolescence alters brain plasticity and behavioral function across the lifespan.

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Poster

082. Animal Cognition and Behavior: Learning and Memory: Hippocampal-Prefrontal Interactions

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 082.14/FFF8

Topic: H.01. Animal Cognition and Behavior

Support: GNSF Grant FR/533/7-274/14

Title: Pre - and postnatal arsenic exposure impairs the behavior, learning, and brain tissue morphology in rats

Authors: ***T. LORTKIPANIDZE**¹, T. BIKASHVILI², N. POCHKHIDZE², N. L. GOGICHAISHVILI¹

¹Ilia State Univ., Tbilisi, Georgia; ²I.Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia

Abstract: Arsenic (As), a ubiquitously distributed metalloid, is an environmental contaminant causing global concern. Chronic intoxication with low doses of arsenicals (consumption of contaminated water) has been connected with various human diseases and was confirmed to have neurological consequences including impaired cognitive development. Despite the extensive knowledge in the field, little is known about the mechanism underlying the effect of prenatal exposure to As on postnatal brain development and the animal behavior. We investigated the effect of As exposure on the behavior and brain morphology of the offspring of rats exposed to As in drinking water before and during pregnancy, as well as for three weeks after parturition. All experiments were performed on Wistar rats. Experimental animals were divided into two groups: Group I - pregnant female rats received water containing As (Sodium arsenite) at concentration of 68mg/L (35 ppm) for 3 weeks before pregnancy, during pregnancy, and three weeks after parturition. Group II - control, received pure drinking water. The offspring, P21 pups, were subjected to following behavioral tests: Open field test, Elevated Plus Maze, Spontaneous alternation behavior test, and Multi-branched maze test. Body weight monitoring showed that at birth there was no significant weight difference between experimental and control groups, while there was a significant difference in postnatal weight gain. Open field test revealed that As-exposed pups were less active and more fearful compared to control ones. Statistically significant differences were revealed between Control and experimental groups in object Novelty Discrimination Index (DIN), Habituation Index according to the locomotor activity, and Displacement Discrimination Index (DID). Thus, recognition memory of As-exposed pups was significantly impaired compared to control animals. Based on the Multi Branch Maze test results, perinatal As exposure induced long-term memory deficit and delay in spatial learning during postnatal development. As-exposed pups spent twice as much time in the maze, and made 4 times more errors than control pups. It has been previously demonstrated that after passing the

blood-brain barrier, the first parenchymal cell type that encounters inorganic arsenicals in the brain are astrocytes. Our morphological and ultrastructural analyses revealed that astrocytes are more susceptible to this metalloid than neurons. While the number and ultrastructure of neurons was slightly altered, astrocytes expressed notable ultrastructural changes in the prefrontal cortex and hippocampus.

Disclosures: **T. Lortkipanidze:** None. **T. Bikashvili:** None. **N. Pochkhidze:** None. **N.L. Gogichaishvili:** None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.01/FFF9

Topic: H.01. Animal Cognition and Behavior

Support: NRF-2012R1A3A1050385

Title: Remote memory and cortical synaptic plasticity require neuronal CCCTC-binding factor (CTCF), a central regulator of epigenetic gene expression

Authors: *H. KIM¹, S. KIM¹, N.-K. YU¹, K.-W. SHIM², J.-I. KIM¹, D. HAN¹, J. CHOI¹, S.-W. LEE¹, D. CHOI¹, M. KIM¹, D.-S. LEE³, K. LEE⁴, N. GALJART⁵, Y.-S. LEE⁶, J.-H. LEE⁷, B.-K. KAANG¹

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Abstract: CCCTC-binding factor (CTCF) is a seven-zinc finger protein, which is well known as a transcription factor and a chromatin regulator. For memory and synaptic plasticity, a dynamic regulation of gene expression is required but, it is not well known how epigenetic mechanisms such as chromatin remodeling, are involved in the memory consolidation and remote memory. To investigate the role of CTCF in remote memory, we generated conditional knockout (cKO) mice in which CTCF is lost in excitatory neurons. The cKO mice showed normal recent memory in the contextual fear conditioning and spatial water maze tasks. However, they showed remarkable impairments in remote memory in both tasks. Underlying the remote memory-specific phenotypes, we observed that loss of CTCF disrupts cortical long-term potentiation (LTP), but not hippocampal LTP. Similarly, we observed that CTCF haploinsufficiency in

inhibitory neurons caused partial impairment of remote memory. Through RNA-sequencing, we observed that CTCF knockdown in cortical neuron culture caused altered expression of genes that are highly involved in cell adhesion, synaptic plasticity, and memory. These results suggest that remote memory storage in the cortex requires CTCF-mediated chromatin regulation in neurons.

Disclosures: **H. Kim:** None. **S. Kim:** None. **N. Yu:** None. **K. Shim:** None. **J. Kim:** None. **D. Han:** None. **J. Choi:** None. **S. Lee:** None. **D. Choi:** None. **M. Kim:** None. **D. Lee:** None. **K. Lee:** None. **N. Galjart:** None. **Y. Lee:** None. **J. Lee:** None. **B. Kaang:** None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

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Program #/Poster #: 083.02/FFF10

Topic: H.01. Animal Cognition and Behavior

Support: Program of Russian Academy of Sciences
Russian Science Foundation Grant 14-25-00072

Title: Epigenetic control of PRKCi and PRKCz genes transcription in rat neurons

Authors: *A. BORODINOVA, M. KUZNETSOVA, P. BALABAN
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Abstract: It is widely accepted that memory consolidation requires *de-novo* transcription of memory-related genes. In general, chromatin rearrangements, particularly histone acetylation, may facilitate gene transcription, but the precise molecular targets are poorly characterized. In the current study we addressed the question of epigenetic regulation of atypical protein kinases (aPKCs) that are critically involved in memory consolidation and maintenance. Using quantitative PCR, we examined the patterns of aPKCs gene expression in rat cultured neurons treated with histone deacetylase (HDAC) inhibitors (trichostatin A, TSA; sodium butyrate, NaB). In cortical cultures TSA induced histone hyperacetylation in the promoter region of *Prkci* gene (confirmed by ChIP assay, n=4), accompanied by a significant delayed elevation of PKCi transcripts quantity (n=8). In parallel, histone hyperacetylation in upstream promoter of *Prkcz* gene (confirmed by ChIP assay, n=4) led to tremendous production of the corresponding PKCz transcripts (n=8) that are almost absent in the brain in resting conditions. In contrast, expression of alternative, brain-specific product of the *Prkcz* gene (PKMz) was significantly decreased after incubation with HDAC inhibitors (19 hrs, n=6). Remarkably, the character of epigenetic regulation of aPKCs was conservative across the neuron populations, since similar expression patterns of protein kinases were observed in rat hippocampal cultures. In an attempt to uncover the origin of these changes, we performed a comprehensive analysis that consisted in silencing

transcription, translation or posttranscriptional processes. Our results suggest that histone hyperacetylation directly activated *Prkci* transcriptional machinery. However, differential expression of PKMz and PKCz, transcribed from downstream and upstream promoters of *Prkcz* gene, depended on protein synthesis. These data might indicate the existence of *Prkcz* promoter competition regulated epigenetically through protein-synthesis dependent mechanisms. Our results suggest that *Prkci* and *Prkcz* genes may represent the targets for epigenetic regulation.

Disclosures: **A. Borodinova:** None. **M. Kuznetsova:** None. **P. Balaban:** None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.03/FFF11

Topic: H.01. Animal Cognition and Behavior

Title: The mechanism of learning memory disability in UTX knock out mouse model

Authors: *L. CHEN¹, M. LIU², W. LI³

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Abstract: Kabuki syndrome is a rare genetic syndrome characterized by a typical facial gestalt, variable degrees of intellectual disability and skeletal abnormalities. Previous genetic studies showed that UTX (lysine-specific demethylase 6A, KDM6A) is one of the main pathogenic genes in Kabuki syndrome. But the mechanism about how UTX gene causes cognitive dysfunction in Kabuki syndrome still remains unclear. Thus, we construct UTX conditional knockout mice to explore the mechanism. UTX knockout mice showed the spatial learning deficits in water maze test, long term potential (LTP) deficits and decrease of dendrites, which remind us that UTX conditional knockout mice can be used as a tool to study the cognitive dysfunction in Kabuki syndrome. We also investigate the electrophysiological mechanism, key target molecular and signaling pathway, and find potential rescue target for drug intervention.

Disclosures: **L. Chen:** None. **M. Liu:** None. **W. Li:** None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.04/FFF12

Topic: H.01. Animal Cognition and Behavior

Support: NSERC
CIHR

Title: A novel role for the histone variant macroH2A in memory formation

Authors: *K. NARKAJ¹, G. STEFANELLI², M. A. BRIMBLE⁴, F. RAMZAN⁵, I. B. ZOVKIC³

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Abstract: Epigenetic modifications are widely recognized for their role in memory formation. Although existing research has focused almost exclusively on DNA methylation and histone post-translational modifications (PTMs), we recently discovered that histone variant exchange, in which canonical histones are replaced by distinct variants, is a novel branch of epigenetics for regulating memory. Our initial work showed that binding of the histone variant H2A.Z is modified by learning, but a potential role of other H2A variants in memory has not been studied. H2A.Z is one of several functionally diverse H2A variants that functions as a memory suppressor. Here, we investigate another potential candidate for memory regulation, histone variant macroH2A (mH2A), which has a widely reported role in regulating gene expression. mH2A is encoded by 2 genes, *H2afy* (encodes mH2A1) and *H2afy2* (encodes mH2A2), both of which are expressed throughout the mouse brain, including the hippocampus, a brain region that is vital for memory formation. To explore the role of mH2A in memory, we used adeno-associated virus (AAV) to knock down either *H2afy* or *H2afy2* in area CA1 and tested mice on an array of hippocampus-dependent memory tasks at the 24-hour and 7-day time points. We found that mice with depleted levels of both mH2A1 and mH2A2 had impaired fear memory 24 hours and 7 days after training, suggesting that both mH2A-encoding genes promote hippocampus-dependent memory formation. To identify the mechanism by which mH2A regulates memory, area CA1 was extracted 30 min after fear conditioning, exposed to mH2A chromatin-immunoprecipitation combined with next-generation sequencing, and compared to genome-wide gene-expression 1h after training, based on time points at which we previously found an association between H2A.Z dynamics and gene expression (Stefanelli et al. 2018 *Cell Reports*). These results support the involvement of histone variant exchange as a novel epigenetic regulator of behaviour and they are the first to show mH2A as a regulator of memory.

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Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.05/FFF13

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant 5R01MH057014-22

Title: Tet1 is expressed as two isoforms with differing roles in the mammalian nervous system

Authors: *G. A. KAAS¹, J. WRIGHT¹, C. B. GREER¹, J. ZHU¹, K. S. CHRONISTER¹, A. Y. JIN¹, A. J. KENNEDY², J. D. SWEATT¹

¹Pharmacol., Vanderbilt Univ., Nashville, TN; ²Bates Col., Lewiston, ME

Abstract: All three Ten-eleven translocation methylcytosine dioxygenase enzymes (TET1-3) have now been implicated in at least some aspect of nervous system function. In particular, studies conducted by our lab and others have found that alterations in TET1 function impact memory performance, disrupt activity-dependent gene expression and alter the intrinsic membrane properties of neurons. However, despite these early findings, the exact role TET1 plays in the nervous system is still not fully understood. Recently, using a number of different experimental techniques, we have discovered that *Tet1* is actually expressed as two distinct mRNA transcripts within the mouse brain. The first, *Tet1 Long (Tet1L)*, encodes for the previously-annotated *Tet1* enzyme which contains a CXXC, Cysteine-rich and DSBH domain. The second, we call *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 first 654 aa of the *Tet1L* enzyme, including the CXXC DNA-binding domain. Using both *in situ* hybridization and qRT-PCR, we have detected both transcripts throughout the mouse brain and found *Tet1S* mRNA levels to be 10-20 times greater than *Tet1L*, depending on the tissue. In addition, the two isoforms also show substantial differences in regards to their transcriptional responses to neuronal activity and sub-cellular protein localization. Similarly, RNAseq data generated in our lab from primary neuron cultures either overexpressing or repressing these *Tet1* isoforms individually also support the notion that these enzymes likely possess distinct cellular functions. Finally, we have developed a number of genetic tools to manipulate both isoforms separately *in vivo* and are currently conducting behavioral, biochemical and electrophysiological experiments to further elucidate the roles of these two enzymes in the context of learning and memory in the mammalian brain.

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Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

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Program #/Poster #: 083.06/FFF14

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant P20GM103423

Title: Reducing tet2 in the ca1 of the hippocampus enhances spatial memory

Authors: *K. ZENGELER¹, X. ZHANG², B. MALACHOWSKY², A. J. KENNEDY²

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Abstract: Active DNA methylation in the hippocampus is necessary for the formation and maintenance 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. DNA demethylation in the hippocampus, driven by ten-eleven translocation 2 (Tet2), negatively regulates memory function at this spatial memory task. Conversely, Tet2 knockdown or knockout enhances 24 hour object location memory, and preserves the fidelity of the memory beyond neurotypical capability. The conditional knockout of Tet2 in CA1 excitatory neurons also coincided with the hypermethylation of genes associated with plasticity and memory, as assessed by whole genome bisulfite sequencing. These data taken together suggest that Tet2 negatively regulates hippocampal-dependent long-term memory by demethylating the genome.

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Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

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Program #/Poster #: 083.07/FFF15

Topic: H.01. Animal Cognition and Behavior

Title: Histone deacetylase inhibitors change methylation patterns and reorganize the chromatin architecture

Authors: *L. CHEN, T. H. SANDERS

Pharmacol. and Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: In recent years neurobiological research has supported increasing associations between memory formation, synaptic plasticity and epigenetic mechanisms (Kennedy and Sweatt, 2016). This study aims to evaluate DNA methylation and chromatin changes by visualizing the methyl binding domain changes in response to HDAC inhibitors in cell culture, slices, and *in vivo*.

DNA is methylated at CpG sites, which often play pivotal roles in regulating gene silencing and chromatin organization. The mobility and pattern of heterochromatin and intensity of DNA methylation inside the cell nucleus can be indicators of epigenetic mechanisms at work. Histone deacetylase (HDAC) and HDAC inhibitors also have a wide range of epigenetic activities; histone deacetylases regulate DNA expression by removing acetyl groups causing the chromatin to be more tightly compacted and making the DNA less accessible for transcription. We tested the effect of sodium butyrate, an HDAC inhibitor, on *MethylRO* brain slices to visualize the fluorescent methyl binding domains.

METHODS

Images of *MethylRO* brain slices were collected to visualize fluorescence in methyl binding domains.

Fig. 1. (See below) These images illustrate the expression of the red fluorescent protein (RFP)-fused-MBD proteins in the striatum (top row) and hippocampus (bottom row).

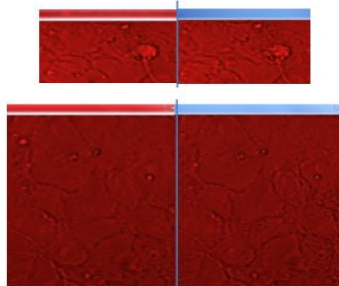
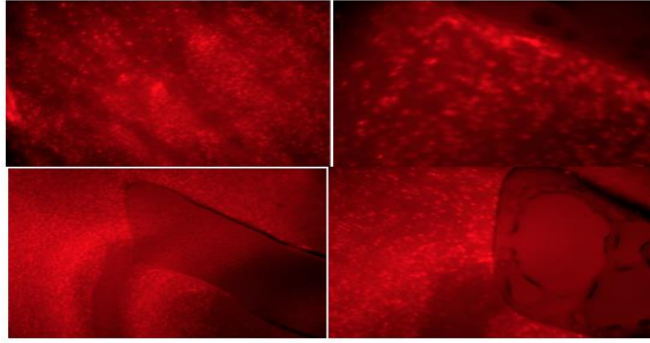
Fig. 2. (See below) The right panel in the image above illustrates the effect of adding sodium butyrate, an HDAC inhibitor. The chromatin appears to migrate toward the nucleus in preparation for transcription.

We found that application of HDAC inhibitors reduced transcription of HDACs, improved behavioral performance, and reorganized chromatin in the nucleus.

References

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Disclosures: L. Chen: None. T.H. Sanders: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.08/FFF16

Topic: H.01. Animal Cognition and Behavior

Support: CONACyT 250870
PAPIIT IN208616
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CB-CONACyT 284748

Title: The inhibition of HDAC induces differential effect on BDNF expression on weak and strong recognition memory

Authors: *G. RAMIREZ MEJIA¹, E. SOTO-REYES², F. BERMUDEZ-RATTONI¹
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Abstract: Memory storage refers to a process where information goes from short- into a long-term form at local synaptic and cellular nodes in the neural circuits that encodes memory. In memory consolidation are involved both gene expression and protein synthesis. It has been demonstrated that epigenetic process such as histone acetylation, helps to stimulate gene

expression of brain derived neurotrophic factor (BDNF), an important molecule related to memory consolidation. Several studies indicate that histone deacetylases (HDACs) could negatively regulate memory formation and maintenance. Although, it has been suggested that hippocampal HDAC inhibition improves memory formation, it remains poorly understood its effects in other areas of the brain. The aim of this work was to study the effect of HDAC inhibition on insular cortex, its role in BDNF expression and its association with memory formation. We used 2-mo C57BL6 mice for all experiments. Animals received intracerebral injections of vehicle or MS-275 (HDAC inhibitor) with a combination of vehicle or K252a (Trk inhibitor) in the anterior insular cortex (AP: +1.4, ML: +-3.3, DV: -4.0) prior to acquisition of weak or strong object recognition-memory task. In order to evaluate BDNF expression extra groups of animals were sacrificed at different time points after the acquisition, while a different groups were assessed at 24 hrs after the learning task for long-term memory. Our results showed that HDAC inhibition in the insular cortex differentially increased histone acetylation (H3K9ac, H4K12ac) and BDNF expression according to stimulus intensity; in the weak acquisition the inhibition of HDAC potentiates memory formation, while in strong condition impairs memory consolidation. This differential effect of HDAC inhibition over memory formation was blocked by inhibition of TrkB activity (BDNF receptor). Our findings proposes that dual effect of HDAC inhibition over memory formation was due to BDNF expression and it was mediated by TrkB receptors.

Disclosures: G. Ramirez Mejia: None. E. Soto-Reyes: None. F. Bermudez-Rattoni: None.

Poster

083. Learning and Memory: Epigenetics

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Topic: H.01. Animal Cognition and Behavior

Support: NIH MH091122

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Start-up funds from Vanderbilt University

Title: Specific reprogramming of the memory-formation blocking gene Hdac2 with an antisense-oligonucleotide

Authors: *C. B. GREER¹, S. G. POPLAWSKI², K. A. GARBETT¹, R. L. MCMAHAN¹, H. B. KORDASIEWICZ³, H. T. ZHAO³, S. T. MOTLEY², D. J. ECKER⁴, A. J. KENNEDY⁵, T. P. MICHAEL², D. J. SWEATT¹

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Abstract: Antisense oligonucleotide (ASO) repression of a target RNA is a powerful means of altering steady-state messenger RNA (mRNA) quantities in cells. ASOs can repress transcript levels for months *in vivo* with a single dose, but the underlying mechanism has not been clearly delineated. We conducted ASO-mediated knockdown of mRNAs in the nervous system by targeting Histone DeAcetylase 2 (*Hdac2*), a gene implicated as a memory-suppressor, *in vitro* and *in vivo*. We observed that an *Hdac2*-targeted ASO not only triggered a reduction in steady-state mRNA and protein levels, but by measuring nascent RNA transcription we determined that it can elicit direct transcriptional suppression of the *Hdac2* gene in neuron-like cells *in vitro*. We found an extra-coding RNA (ecRNA) transcribed from the *Hdac2* gene in neurons. ecRNAs are unspliced transcripts that initiate upstream and terminate downstream of their originating gene. They regulate mRNA expression by preventing repressive DNA methylation. Because ASOs could possibly bind and degrade ecRNAs as they also contain the mRNA target sequence, we measured ecRNA transcription after ASO treatment. We found that just like the coding transcript, transcription of *Hdac2* ecRNA is repressed by the ASO. Furthermore, ASO treatment correlated with altered DNA cytosine methylation of the *Hdac2* gene measured by bisulfite sequencing. From *in vivo* studies, we observed that a single dose of the *Hdac2*-targeted ASO delivered intraventricularly into the CNS of mice achieved steady-state diminution of *Hdac2* mRNA levels that lasted 4 months *in vivo*. This reduction in *Hdac2* corresponded with memory enhancement in a novel object recognition test. Overall, these findings indicate the discovery of a mechanism that explains the long-lasting action of ASO mediated repression of *Hdac2*, namely transcriptional suppression through epigenetic reprogramming of the target gene mediated by an ecRNA.

Disclosures: C.B. Greer: None. S.G. Poplawski: None. K.A. Garbett: None. R.L. McMahan: None. H.B. Kordasiewicz: A. Employment/Salary (full or part-time); Abbott. H.T. Zhao: A. Employment/Salary (full or part-time); Abbott. S.T. Motley: None. D.J. Ecker: A. Employment/Salary (full or part-time); Abbott. A.J. Kennedy: None. T.P. Michael: None. D.J. Sweatt: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

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Program #/Poster #: 083.10/FFF18

Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH103102-04
1R01MH115059-01

Title: DNA methylation profiles underlie neuronal allocation dynamics in the hippocampus

Authors: *S. ODELL¹, F. TAKI², R. J. CHEN³, O. B. LEVINE³, S. KLEIN², A. SHARMA², J. GAL TOTH², K. E. PLEIL², M. TOTH¹

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Abstract: One of the biggest gaps in knowledge in the memory field is understanding how the brain encodes and processes the large amounts of information it receives, efficiently. The consensus in the field is that episodic memories are stored in various brain regions, including the hippocampus, through sparse coding, in which small ensembles of the overall population of neurons are activated during a given context exposure. Yet, the mechanism that dictates which cells are recruited for allocation during a sparse coding event is largely elusive. It is thought that allocation is dependent on intrinsic factors because neurons with a high level of excitability are preferentially recruited during context exposure. Factors that increase excitability include the transcription factor CREB, but it is not known how CREB and other excitability-related molecules are regulated and how their interactions contribute to allocation. We introduce a model in which epigenetic, specifically DNA methylation, changes at specific genomic regions dictate allocation dynamics and coding in the hippocampus. We find that genetically shifting methylation selectively at these allocation related regions, results in altered hippocampal-dependent behaviors, including changes in spatial navigation, pattern separation, and nonspatial object discrimination. Our model helps explain the molecular aspects of the elusive process of neuron allocation and sparse coding of experiences.

Disclosures: S. Odell: None. F. Taki: None. R.J. Chen: None. O.B. Levine: None. S. Klein: None. A. Sharma: None. J. Gal Toth: None. K.E. Pleil: None. M. Toth: None.

Poster

083. Learning and Memory: Epigenetics

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Program #/Poster #: 083.11/FFF19

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH057014
NSF Graduate Research Fellowship
NIH Grant T32 DK07563

Title: Methylation dynamics of neuronal Fos gene expression

Authors: *S. GOLEVA¹, C. B. GREER², G. A. KAAS², J. D. SWEATT³

²Pharmacol., ¹Vanderbilt Univ., Nashville, TN; ³Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Epigenetic mechanisms are regulatory modifications that affect gene expression without changing the DNA sequence. Epigenetic mechanisms, such as DNA methylation, are critical for normal cognitive processes, including learning and memory, and their dysregulation can contribute to memory-related disorders. DNA cytosine methylation is dynamically catalyzed by DNA methyltransferases (DNMTs). Active demethylation of methylated cytosines is catalyzed by ten-eleven translocases (TETs). Increased promoter cytosine methylation has been shown to be inversely correlated with mRNA expression in adult neurons. In the present studies, we focus on the methylation dynamics of the neuronal activity marker gene Fos, an immediate early gene whose expression increases transiently *in vivo* upon neuronal activation such as memory formation and learning. The exact spatial and temporal methylation dynamics in regulating Fos expression have yet to be elucidated. Here we investigated how manipulating DNA methylation activity affects Fos gene expression during neuronal activation using KCl in differentiated N2a cells and primary cortical neurons. To explore the effects of inhibiting active methylation, we used RG108 to inhibit DNMT catalytic activity. We show that the immediate increase in Fos mRNA expression in response to neuronal activation is blunted by DNMT inhibition. To confirm the effects of inhibiting DNMT genetically, we designed DNMT3a/DNMT1 antisense oligonucleotides to decrease DNMT gene expression. To explore the effects of inhibiting active demethylation, we knocked down Tet2 expression by using a transcriptional-activator like effector fused to the transcriptional repressor domain SID4X that targets Tet2. Our results showed that this construct downregulates Tet2 expression by around 50%, which decreases active demethylation. We show that Tet2 knockdown increases baseline Fos expression in dN2a cells and amplifies KCl-induced increases in Fos expression. To determine if artificially methylating Fos DNA would be sufficient to alter Fos mRNA expression, we used a catalytically dead Cas9 nuclease fused to the DNMT3a catalytic domain. We cotransfected this construct with guide RNAs to target DNMT3a to the Fos promoter. Our results showed that artificially methylating the Fos promoter increases Fos mRNA expression, which is opposite to the canonical idea of promoter methylation blocking mRNA expression. The present studies provide a strategy to clarify the relationship between DNA methylation and mRNA activity at a specific immediate early gene, the correct expression of which is necessary for memory formation and learning.

Disclosures: S. Goleva: None. C.B. Greer: None. G.A. Kaas: None. J.D. Sweatt: None.

Poster

083. Learning and Memory: Epigenetics

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Program #/Poster #: 083.12/FFF20

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH057014

NIH Grant MH107254
NIH Grant GM007347

Title: Consequences of histone variant overexpression in the mouse hippocampus

Authors: *B. EISELE¹, I. B. ZOVKIC², J. D. SWEATT³

¹Vanderbilt Univ., Nashville, TN; ²Psychology, Univ. of Toronto Mississauga, Mississauga, ON, Canada; ³Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Changes in gene expression are essential for formation and consolidation of memories. Epigenetic mechanisms, which regulate gene expression by altering chromatin structure, have recently emerged as critical regulators of memory. Nucleosomes (octamers of histone proteins H2A, H2B, H3, and H4) bind DNA and generally act as barriers to transcription. These nucleosomes are subject to histone subunit exchange, wherein a canonical histone is replaced by an atypical variant. This exchange alters nucleosome-DNA binding, providing an avenue for the control of transcriptional availability of DNA and gene expression. Histone variants differ from their canonical counterparts in that their incorporation is gene-replication-independent. This characteristic is of particular significance in neurons, which are post-mitotic and rely on mechanisms to alter gene expression independently of cell division. Innovative studies have recently discovered that histone variant exchange regulates memory consolidation (Zovkic et al., 2014; Maze et al., 2015; Yang et al., 2016). This exciting discovery points to a critical role for regulation of nucleosome subunit composition in cognition. Previous work has shown that depletion of histone variants in the dorsal hippocampus of mice leads to alterations in contextual fear memory (Zovkic et al., 2014). However, we have yet to evaluate the functional consequences of histone variant overexpression, and its influence on memory-associated gene expression patterns and associative learning. This investigation is of particular significance, as previous work shows that histone variant *macroH2A1* is overexpressed in patients and mouse models of Huntington's disease, a neurodegenerative condition associated with severe cognitive decline (Hu et al., 2011). Our results demonstrate the effectiveness of utilizing adeno-associated viral (AAV) gene delivery systems to enhance both gene and protein expression of H2A variants *macroH2A1*, *macroH2A2*, and *H2A.Z* in the mouse hippocampus *in vivo*. Additionally, we present results of ongoing experiments investigating histone overexpression on both associative fear memory and on learning-associated transcriptional states. Our results point to complex interactions between histone variants to regulate learning-induced gene expression patterns.

Disclosures: B. Eisele: None. I.B. Zovkic: None. J.D. Sweatt: None.

Poster

083. Learning and Memory: Epigenetics

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Program #/Poster #: 083.13/FFF21

Topic: H.01. Animal Cognition and Behavior

Support: T32 GM07628

NIH 5R01MH057014-22

Title: DNA methylation regulates neuronal intrinsic excitability through altered gene expression of small conductance calcium-gated (SK) channels

Authors: ***J. BROWN**¹, G. A. KAAS¹, C. B. GREER¹, J. WRIGHT¹, D. G. WINDER², J. D. SWEATT³

¹Pharmacol., ²Vanderbilt Univ., Nashville, TN; ³Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Learning and memory depend on activity-regulated neuronal plasticity. Integration and storage of memories involve alterations in synaptic strength and membrane excitability that are driven by changes in gene expression. We hypothesize that epigenetic modifications, including DNA methylation, are possible mechanisms for memory associated regulation of gene expression. Recent published studies support DNA methylation as a regulator of site-specific synaptic plasticity and neuron-wide synaptic scaling. However, an association between DNA methylation and intrinsic plasticity, an additional form of neuronal plasticity, is less defined. Previous data from our lab showed DNA methylation is involved in regulating small conductance calcium dependent potassium (SK) channel gene expression underlying the medium AHP (mAHP). Using a small molecule inhibitor and targeted antisense oligonucleotides (ASOs), our lab has shown that inhibition of DNA methyltransferases (DNMTs), the enzymes that catalyze DNA methylation, results in increased intrinsic excitability, which manifests as an increase in AP frequency and decreased mAHP waveform in response to depolarizing current. This increased excitability required TET1, the enzyme involved in demethylation of DNA, and was not potentiated with the addition of an SK channel-specific blocker, apamin. These results suggest a direct link between DNA methylation inhibition and intrinsic plasticity through regulation of SK channel expression. With the use of two gene editing tools, Transcription Activator Like Effectors (TALEs) and CRISPR-dCas9 constructs, our lab has demonstrated the ability to modulate gene expression and methylation in Neuroblastoma (N2A) cells and cortical neurons. These tools will further elucidate this relationship by altering the expression and methylation of SK channel genes in primary neurons. Following transfection into neurons, changes in intrinsic excitability will be measured using whole-cell patch electrophysiology. Direct infusion of these constructs into the mouse hippocampus will determine the effects of DNA methylation of these SK channels on cognitive function including changes in learning and memory. These tools will provide evidence for the direct effects of DNA methylation on altering SK channel gene expression and a readout of the functional downstream effects.

Disclosures: **J. Brown:** None. **G.A. Kaas:** None. **C.B. Greer:** None. **J. Wright:** None. **D.G. Winder:** None. **J.D. Sweatt:** None.

Poster

083. Learning and Memory: Epigenetics

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Program #/Poster #: 083.14/FFF22

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH57014
T32 GM07628

Title: Regulation of synaptic downscaling via dna methylation of arc

Authors: *B. C. COLEMAN, G. KAAS, D. SWEATT
Vanderbilt Univ., Nashville, TN

Abstract: Our understanding of the mechanisms that lead to the formation of a memory has grown significantly over the past few decades. One such mechanism is homeostatic plasticity, which can be defined as a neuron's ability to regulate its excitability at the whole cell level to maintain signal specificity. Synaptic scaling, increasing (synaptic upscaling) or decreasing (synaptic downscaling) the strength of synapses cell-wide by changing the concentration of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA receptors) present on the postsynaptic neuron, is one way neurons accomplish homeostatic plasticity. The activity-regulated cytoskeleton-associated (Arc) protein is critical for synaptic downscaling through its role in AMPAR endocytosis during prolonged neuronal activity. DNA methylation has emerged as an exciting and reversible mechanism that neurons may use to accomplish the long-term storage of a memory. With Arc playing an imperative role in synaptic downscaling, and recent evidence for the role of DNA methylation in homeostatic plasticity, we will provide evidence that methylation of *Arc* regulates synaptic downscaling. Our preliminary evidence indicates that DNA methylation can regulate *Arc* expression. Thus, treating mouse primary cortical neurons with a DNMT3a antisense oligonucleotide (ASO) increases *Arc* mRNA levels. To pinpoint any regions where DNA methylation may be altered during neuronal activity, we are treating mouse primary cortical neurons with KCl and then performing bisulfite sequencing. Once identified, in order to manipulate the methylation of *Arc* in a targeted fashion, we are in the process of developing transcription activator-like effectors (TALEs) containing either a DNA methyltransferase or ten-eleven translocation catalytic domain that will allow methylation or demethylation of specific regions of the *Arc* gene. Our lab has preliminary evidence showing that targeting a TALE with a DNMT domain to the *Arc* promoter can decrease levels of *Arc* mRNA. We have also developed TALEs containing a VP64 or Sid4x effector domain targeted to the *Arc* promoter that are capable of increasing and decreasing *Arc* expression, respectively. Ultimately, we aim to show that altering the methylation of *Arc* will impact synaptic downscaling, by transfecting primary neurons with the aforementioned TALEs and recording mini excitatory post synaptic currents

(mEPSCs) using the whole cell voltage clamp technique. We anticipate that these experiments will provide increasing evidence for the importance of DNA methylation in homeostatic synaptic plasticity.

Disclosures: **B.C. Coleman:** None. **G. Kaas:** None. **D. Sweatt:** None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

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Program #/Poster #: 083.15/FFF23

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R01MH057014-23

Title: Histone H3 lysine K4-trimethyl breadth changes in a contextual fear-conditioning paradigm

Authors: ***B. COLLINS**¹, C. B. GREER², J. D. SWEATT²
²Pharmacol., ¹Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Mutations of histone 3 lysine 4 (H3K4) methylation modifying enzymes such as KMT2A and KDM5C are associated with intellectual disability and impaired learning in behavioral conditioning paradigms, suggesting that methylation at this site is an essential epigenetic component of cognition. Trimethylation of H3K4 (H3K4me3) is predominantly found in symmetric ~1-kilobase regions centered at transcription start sites (TSSs) of active genes. However, a subset of H3K4me3-enriched regions, termed H3K4me3 broad domains, exhibit a wider distribution skewed downstream of the TSS. While H3K4me3 broad domains have been previously shown to mark genes important for cell identity and exhibit marks of transcriptional elongation, their function is largely unknown, particularly in non-dividing cells such as neurons. Using previously published H3K4me3 ChIP-seq and RNA-seq data from the CA1 subregion of mice hippocampi, we find that genes marked by H3K4me3 broad domains in neurons of mice demonstrate an enrichment in neuron-specific functions, as previously reported for other somatic cells. Further, H3K4me3 breadth is positively correlated with gene expression levels such that H3K4me3 broad domains are more highly expressed than narrower regions of H3K4me3. To begin investigating a potential role for H3K4me3 breadth in learning and memory, this work presents an analysis of mice undergoing contextual fear-conditioning (CFC). Genes exhibiting significant H3K4me3 broadening with contextual and associative learning exhibit increased changes in expression relative to other genes and are enriched in learning- and memory-related functions via Gene Ontology analysis. These results suggest a potential role for H3K4me3 broadening in learning and may offer further directions in investigating how dysregulation of H3K4 methylation machinery leads to intellectual disability syndromes.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: Westpac Future Leaders Scholarship 2017

5RO1MH105398

5RO1MH109588-03

APP1033127

Title: Profiling activity-dependent small non-coding RNA activity in the mouse brain

Authors: *L. J. LEIGHTON, W. WEI, J. EDSON, Q. ZHAO, J. WANG, T. W. BREDY
Queensland Brain Inst., St Lucia, Australia

Abstract: Small non-coding RNAs are essential components of metabolic, signaling and regulatory pathways in diverse cell types, including neurons. While most classes of small non-coding RNA are known to be expressed in the mammalian brain, the functions of most individual small RNAs are yet to be determined. Attempts to functionally characterize them are hindered by a lack of information about their cell type specificity, subcellular localization, and response to neuronal activation. We profiled small non-coding RNA expression from the mouse hippocampus at two timepoints (immediate and 90 minutes) following contextual fear conditioning, and used subcellular fractionation to compare their expression level in the nucleus and cytoplasm. We have identified dozens of small RNAs (including micro-RNAs, Piwi-interacting RNAs, transfer RNA fragments, and small nucleolar RNAs) which are differentially expressed following behavioural training and consequently implicated in fear-related learning processes. These include a number of novel small RNAs which likely have brain-specific expression patterns. Additionally, we have identified small RNAs which shuttle between the nuclear and cytoplasmic compartments under conditions of neuronal activation. Ongoing work in our laboratory is resolving ambiguity surrounding the origin and function of some neuronal small RNAs (particularly Piwi-interacting RNAs) using advanced molecular techniques such as 3' end-selective sequencing to confirm their identity with greater precision. Our data implicates previously unknown small RNAs in synaptic plasticity, learning and memory, and will ultimately lead to a clearer understanding of their functions in the mammalian brain.

Disclosures: L.J. Leighton: None. W. Wei: None. J. Edson: None. Q. Zhao: None. J. Wang: None. T.W. Bredy: None.

Poster

083. Learning and Memory: Epigenetics

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Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH105398
5R01MH109588-03
APP1033127

Title: The accumulation of N6-methyl-2'-deoxyadenosine in DNA drives activity-induced gene expression and is required for the extinction of conditioned fear

Authors: ***T. W. BREDY**, X. LI, W. WEI, P. MARSHALL, Q. ZHAO, L. LEIGHTON, E. ZAJACZKOWSKI
Queensland Brain Inst., St Lucia, Australia

Abstract: Here we report that the recently discovered mammalian DNA modification N6-methyl-2'-deoxyadenosine (m6dA) is dynamically regulated in primary cortical neurons and accumulates within promoters and coding sequences of activated neurons within the prefrontal cortex of adult C57/B16 mice following fear extinction learning. The deposition of m6dA is generally associated with an increase in the genome-wide occupancy of the putative m6dA methyltransferase, N6amt1, and correlates with an increase in fear-extinction learning induced gene expression. At the brain-derived neurotrophic factor (BDNF) P4 promoter, m6dA is associated with an open chromatin state and the recruitment of the activating transcription factor Yin-Yang 1 and RNA polymerase II, which are necessary for activity-induced BDNF gene expression and required for the extinction of conditioned fear. These findings expand the scope of DNA modifications in the adult brain and highlight DNA m6dA as novel neuroepigenetic mechanism associated with activity-induced gene expression and the formation of fear extinction memory.

Disclosures: **T.W. Bredy:** None. **X. Li:** None. **W. Wei:** None. **P. Marshall:** None. **Q. Zhao:** None. **L. Leighton:** None. **E. Zajaczkowski:** None.

Poster

083. Learning and Memory: Epigenetics

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Program #/Poster #: 083.18/GGG2

Topic: H.01. Animal Cognition and Behavior

Support: 5RO1MH105398
5RO1MH109588-03
APP1033127

Title: Potential dual function of ADAR1 as an RNA editing enzyme and DNA binding protein in the activity-dependent regulation of gene expression and adaptive behaviour in the mouse

Authors: *P. R. MARSHALL¹, Q. ZHAO², X. LI², W. WEI², E. L. ZAJACZKOWSKI³, L. LEIGHTON², T. BREDY²

¹Queensland Brain Inst., Univ. of Queensland, St Lucia, Australia; ²Queensland Brain Inst., Brisbane, Australia; ³Queensland Brain Inst., St Lucia, Australia

Abstract: RNA editing has been correlatively linked to behaviour in organisms ranging from flies to humans, with the highest levels of the enzymes mediating this process found in primates, humans, and in some instance in a brain-specific manner. Mechanistically, this occurs through the deamination of specific base nucleotides, including adenosine in the case of the adenosine deaminase (ADAR). However, not all variants of ADAR appear to operate solely on RNA. For example, ADAR1 can also bind to DNA but the functional relevance of this capacity in the brain remains relatively unexplored. In order to begin to assess the potential RNA-independent function of ADAR1 in neurons, and in the context of behavioural adaptation, ADAR1 ChIP-seq was performed on activated primary cortical neurons (PCN's) in vitro, and on cortical neurons derived from adult mice subjected to behavioural training. We have discovered that ADAR1 binds a number of targets on DNA in an activity-dependent manner. In addition, we have found that lentiviral-mediated knockdown of ADAR1 in the infralimbic cortex leads to an enhancement of fear-related memory. It remains to be seen to what extent this effect on memory is mediated primarily by RNA editing or by ADAR1's capacity to bind to DNA.

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Poster

083. Learning and Memory: Epigenetics

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Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH105398
5R01MH109588-03
APP1033127

Title: Spatially distinct patterns of RNA modifications in neurons following fear extinction learning in mice

Authors: *S. U. MADUGALLE^{1,2}, X. LI^{1,2}, T. W. BREDY^{1,2}

¹Queensland Brain Inst., St Lucia, Australia; ²Univ. of Queensland, St Lucia, Australia

Abstract: RNA modification has recently emerged as an important mechanism to control RNA metabolism by promoting RNA localisation, translation and/or RNA degradation in neurons. Previously, we demonstrated a functional relationship between the RNA modification, N⁶-methyladenosine (m⁶A), and fear-related learning and memory; however, whether m⁶A governs other forms of learning, such as fear extinction remains unknown. In the current study, we have found increased expression of the RNA methyltransferase Mettl3 within the infralimbic prefrontal cortex (ILPFC) of mice in response to fear extinction learning, which is associated with the accumulation of synaptically enriched m⁶A modified RNA. Furthermore, we have also identified an RNA binding protein whose motif is enriched in m⁶A modified RNA and that translocates from the nucleus to the synapse upon neural activation. These findings suggest a role for RNA methylation in regulating experience-dependent patterns of subcellular compartmentalization of RNA, which could have a significant impact on local translation events in response to fear extinction learning. Ongoing experiments are being performed to determine the functional influence of this process on the formation and stability of fear extinction memory.

Disclosures: S.U. Madugalle: None. X. Li: None. T.W. Bredy: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.20/GGG4

Topic: H.01. Animal Cognition and Behavior

Support: ARC Grant DP180102998
NIH Grant 1R21MH113062

Title: Bioorthogonal metabolic labelling of nascent RNA in neurons improves the sensitivity of transcriptome-wide profiling

Authors: *E. L. ZAJACZKOWSKI¹, Q. ZHAO¹, Z. ZHANG¹, X. LI¹, W. WEI¹, P. R. MARSHALL¹, L. J. LEIGHTON^{1,2}, S. NAINAR², C. FENG², R. C. SPITALE², T. W. BREDY¹
¹Queensland Brain Inst., St Lucia, Australia; ²Dept. of Pharmaceut. Sci., Univ. of California Irvine, Irvine, CA

Abstract: Despite significant advances in sequencing homogenous cell populations and single cells, current techniques for profiling activity-induced molecular changes fail to differentiate between steady-state (i.e. pre-stimulus) RNA and nascent (i.e. stimulus-induced) RNA. Here, we present the utility of a new method that allows for selective enrichment and visualization of nascent RNA. To accomplish this, the method employs the use of uracil phosphoribosyltransferase (UPRT), an enzyme derived from *Toxoplasma gondii*, that drives the incorporation of a chemically-modified nucleobase, 5-ethynyl-uracil (5E-Uracil), into RNA that is being transcribed. UPRT overexpression within a restricted population of cells enables spatial control over RNA tagging whilst the addition of the analog 5E-Uracil provides temporal control. Nascent RNA that contains 5E-Uracil can then be visualized or isolated using the well-characterised Cu(I)-catalysed alkyne-azide cycloaddition reaction, which can append either a fluorophore or biotin group onto the nascent RNA, respectively. Following nascent RNA sequencing of stimulated (KCl+) and unstimulated (KCl-) mouse primary cortical neurons, we observe a significant improvement in the sensitivity of differential gene expression analysis, including the detection of several plasticity-related genes that could not be identified using standard total RNA-seq. We are currently in the process of optimising these methods for in vivo RNA labelling during behavioural tasks and anticipate that our work will contribute towards a better understanding of the differential contributions of steady-state and nascent RNA in various activity-related scenarios, especially those during learning and memory formation.

Disclosures: E.L. Zajackowski: None. Q. Zhao: None. Z. Zhang: None. X. Li: None. W. Wei: None. P.R. Marshall: None. L.J. Leighton: None. S. Nainar: None. C. Feng: None. R.C. Spitale: None. T.W. Bredy: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.21/GGG5

Topic: H.01. Animal Cognition and Behavior

Support: VA Grant NURD-013-16S

Title: Epigenetic mechanisms linking diabetes and synaptic dysfunction and the role of physical exercise

Authors: *J. WANG^{1,2}, M. VARGHESE¹, W. ZHAO^{1,2}

¹Icahn Sch. of Med. At Mount Sinai, New York, NY; ²James J. Peters Veterans Affairs Med. Ctr., Bronx, NY

Abstract: Despite worldwide prevention efforts, the incidence of type II diabetes (T2D) continues to rise, especially among the elderly. Mounting evidence suggests a causative role of T2D in the onset and progression of dementia. Emerging studies have demonstrated that diabetes-associated chromatin modifications pertinent to epigenetic mechanisms play an important role in brain pathophysiology. We recently found significantly altered expression of select chromatin modification enzymes, including histone deacetylases (HDAC) class IIa, in postmortem brains of T2D subjects, and demonstrated that these changes coincided with altered expression of proteins implicating synaptic plasticity impairments. The present study is designed to test the hypothesis that elevated expression of select HDAC IIa, specifically, HDAC5 in the T2D brain may contribute to cognitive decline by altering the expression of mitochondrial and synaptic genes, resulting in cellular energy metabolism dysregulation, and neuronal and dendritic spine structure/activity impairments, ultimately leading to cognitive dysfunction. We are using shRNA specific for HDAC5 to establish cause-effect relationship between HDAC5 and mitochondrial respiratory dysregulation and synaptic plasticity impairments in primary cortico-hippocampal neurons. Moreover, based on our observation that physical exercise for two hours per day for 7 days in wild type healthy mice significantly reduced the expression of HDAC5 in the brain and this change is associated with increased expression of brain derived neurotrophic factor (BDNF) and increased expression of synaptic proteins that are important for learning and memory. We are currently testing whether physical exercise is also effective to prevent and/or reverse T2D-induced, HDAC5-mediated mitochondrial dysfunction and synaptic impairment. Our study will provide experimental evidence that HDAC5 mechanistically link T2D and neuropathological changes in the brain, and provide potential novel targets for therapeutic development.

Disclosures: J. Wang: None. M. Varghese: None. W. Zhao: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.22/GGG6

Topic: H.01. Animal Cognition and Behavior

Support: Weston Brain Institute

Title: Bidirectional amelioration of object and spatial memory deficits by the lysine acetyltransferase PCAF in the 3xTG mouse model of Alzheimer's disease

Authors: *S. D. CREIGHTON¹, A. DESIMONE¹, K. H. JARDINE¹, M. ZMETANA¹, S. CASTELLANO², C. MILITE², G. SBARDELLA², B. D. WINTERS¹

¹Psychology, Univ. of Guelph, Guelph, ON, Canada; ²Med. Chem., Univ. of Salerno, Salerno, Italy

Abstract: The acetylation of histone and non-histone proteins by lysine acetyltransferases (KATs) supports many mnemonic processes. As there is growing evidence that dysregulation of acetylation plays a role in cognitive deficits and neuropathology in Alzheimer's disease (AD), increasing KAT activity has emerged as a promising therapeutic strategy. However, acetylation patterns in AD are likely multifarious and memory deficits may not always be ameliorated by simply activating KATs. Indeed, the KAT, PCAF, may function atypically in AD. While PCAF activation enhances memory in normal rodents, in AB-treated rats, PCAF inhibition or KO attenuates AD-like cognitive deficits, suggesting that PCAF activity may actually be detrimental. By longitudinally evaluating the effects of acute PCAF activation and inhibition on object recognition (OR) memory at 3, 6, 9, and 12 months of age, we show that PCAF bidirectionally regulates cognition in male and female triple transgenic (3xTG) AD mice. At 3 and 6 months of age, prior to the development of OR deficits, the PCAF activator, SPV-106, enhanced short- (5min) and long-term (3h) OR, whereas the PCAF inhibitor, embelin, impaired. At 9 months of age, when OR impairment was first observed, SPV-106 ameliorated the long-term OR deficit. At 12 months of age, however, SPV-106 induced a short-term OR impairment, while embelin ameliorated the long-term OR deficit. A similar, albeit accelerated, pattern of results was observed for spatial memory using the object location task (OL). OL impairments were first observed at 3 months of age. At both 3 and 6 months of age, SPV-106 ameliorated short- and long-term OL deficits. At 9 months of age, SPV-106 had no effect on OL, whereas embelin ameliorated short- and long-term OL deficits. This work reveals a complex role for PCAF throughout AD progression, initially benefitting memory but detrimental as neuropathology becomes more severe. Therefore, memory deficits in AD may not always be ameliorated by KAT activation, and greater insight into the interactions between KATs, AD pathology, and cognition is necessary for the future success of epigenetic therapies.

Disclosures: S.D. Creighton: None. A. Desimone: None. K.H. Jardine: None. M. Zmetana: None. S. Castellano: None. C. Milite: None. G. Sbardella: None. B.D. Winters: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.23/GGG7

Topic: H.01. Animal Cognition and Behavior

Support: NIDA- DP1 DA042232

Title: Cell-type specific transcriptomic signatures induced by THC in the mouse adolescent brain

Authors: *P. MONTILLA-PÉREZ, A. IEMOLO, Q. MA, F. TELESE
UCSD, San Diego, CA

Abstract: Chronic and heavy marijuana use in adolescence has been associated with impaired cognitive functions such as learning, memory, attention and decision-making. Recent evidence suggests that other factors could predispose teenagers who use marijuana to cognitive impairments, including genetic predisposition and childhood trauma. It is thought that dysregulation of epigenetic pathways and gene expression patterns could underlie these behavioral outcomes, as indicated by animal studies using crude brain extracts. However, little is known about the effects of marijuana on epigenetic and transcriptional pathways in distinct neuronal subtypes involved in cognition. In our study, we sought to address this challenge by using INTACT (isolation of nuclei tagged in specific cell types). In this method, a Cre construct drives the expression of a GFP tag on the nuclear envelope allowing the immuno-isolation of nuclei from distinct cell-types and the genome-wide analysis of transcriptional and epigenetic changes. We generated lines carrying the INTACT construct in Camk2a-excitatory and Parvalbumin (PV)-inhibitory neurons using WT or Heterozygous Reeler mice (HRM). Reelin is a strong candidate gene in the etiology of multiple psychiatric disorders and we previously showed that it regulates epigenetic pathways underlying memory formation (Telese et al., *Neuron*, 2015). Thus, we generated nuclear RNA-seq datasets of distinct neuronal populations isolated from mice that received daily injections of $\Delta 9$ -tetrahydrocannabinol (THC) during the adolescent period (P28-P48). This drug treatment was followed by two weeks of abstinence. In a parallel study, we have shown that THC chronic administration is associated with deficits in working memory and social interaction. By analyzing transcriptomes, we have identified gene regulatory networks dysregulated by THC and we have gained insight into how decreased Reelin levels might affect the cellular response to THC in adolescence. We are conducting similar experiments to identify epigenetic signatures that correlate with the transcriptional changes in different neuronal subtypes.

Disclosures: P. Montilla-Pérez: None. A. Iemolo: None. Q. Ma: None. F. Telese: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.24/GGG8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DP1DA042232

Title: The potential role of reelin signaling in cannabis-induced behavioral changes

Authors: *A. IEMOLO, F. TELESE
UCSD Sch. of Med., San Diego, CA

Abstract: Accumulating evidence suggests that chronic, heavy marijuana use in teenagers is associated with long-term behavioral alterations, including memory deficits and psychotic-like behaviors. It is thought that additional factors, such as genetics and environment, might contribute to these effects. Here, we hypothesize that individuals carrying genetic factors that confer vulnerability to psychotic behaviors might be more susceptible to potential long-term detrimental effects of marijuana abuse during adolescence. Many genes have been identified as candidate for schizophrenia and related psychotic behaviors, such as the Reelin gene. Reelin, a large glycoprotein of the extracellular matrix, plays a key role in neuronal migration during brain development and in synaptic plasticity in the mature brain. Reduced expression of Reelin has been observed in studies of post-mortem brains of individuals affected by psychiatric disorders, including schizophrenia. Therefore, in this study, we used the heterozygous Reeler mice (HET) as a mouse model of genetic predisposition to schizophrenia in order to examine the behavioral effects of high doses of Δ^9 -tetrahydrocannabinol (THC), a major psychoactive component of cannabis, during the adolescent period. WT and HET mice of both genders (10-15 subjects per group) received daily injections of either vehicle or THC (10 mg/kg) for 21 days (from postnatal day (PD) 28 to PD 48), and were then evaluated with a battery of behavioral tests (light-dark, open-field, locomotion, novel object recognition, social test) after 15 drug-free days. Our findings were replicated across separate experimental groups. Chronic administration of THC during adolescence led to mild long-term impairments in novelty preference and sociability in male and female mice of both genotype to a similar extent. Interestingly, only in the female HET mice, chronic THC administration resulted in increased locomotor activity and reduced anxiety-like behaviors in the open field test, suggesting that reduction in Reelin expression in individuals that are exposed to heavy, chronic doses of THC during adolescence may predispose to different aspects of psychotic-like behaviors, including hyperlocomotion and behavioral disinhibition. Further studies are currently in progress to investigate the effects of chronic THC in other behavioral assays, such as the pre-pulse inhibition and the marble-burying tests. Finally, we are

analyzing the epigenomic changes induced by THC in distinct neuronal subtypes during adolescence in order to assess the underlying molecular mechanisms.

Disclosures: F. Telese: None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.25/GGG9

Topic: H.01. Animal Cognition and Behavior

Support: NIDA- DP1 DA042232

Title: The effects of cannabinoids on neuronal activity-dependent transcription in primary cortical neurons

Authors: *E. FLORIO, W. JUNNENG, F. TELESE

Univ. of California San Diego, San Diego, CA

Abstract: Endocannabinoids (eCBs) are lipid messengers highly expressed throughout the central nervous system in which they act as key modulators of synaptic function and are implicated in a wide range of neural functions, including cognition, emotions, feeding behaviors, motor control and pain. Extensive research has demonstrated that eCBs and synthetic cannabinoids, such as Δ^9 -tetrahydrocannabinol (THC), suppress the release of neurotransmitters at excitatory and inhibitory synapses via a retrograde signaling that is mediated by presynaptic cannabinoid receptors (CB1R). Emerging literature suggests that cannabinoids can modulate neuronal function by a non-retrograde signaling; however, the underlying mechanisms remain largely unknown. In this study, we investigate the hypothesis that cannabinoids might influence neuronal activity-dependent transcription, which is a major mechanism underlying synaptic plasticity. We use primary neuronal cultures that are isolated from embryonic mouse brains and we measure neuronal-activity dependent transcription by RT-qPCR following the induction of membrane depolarization in the presence of KCl. Using this system, we tested the effects of different synthetic agonists of the CB1R, including THC and cannabidiol (CBD), which are the major psychoactive components of marijuana. In basal conditions, cannabinoids do not affect the transcription of neuronal activity-dependent genes. However, THC and CBD suppress the transcriptional activation of neuronal activity-dependent genes (e.g. Fos, NPas4, Homer1) induced by KCl-mediated membrane depolarization. We observe a transcriptional repressive activity of cannabinoids after 48-hours or 1-hour pretreatment with 5 μ M THC or 5 μ M CBD. This inhibitory effect is still present when primary neurons are co-treated with a CB1R antagonist. This preliminary data suggests that a CB1R-independent mechanism might be implicated in the inhibition of neuronal activity-dependent genes mediated by cannabinoids. In

an effort to gain further insight in this novel pathway, we are performing genome-wide transcriptional profiling by RNA-seq to identify gene networks regulated by cannabinoids.

Disclosures: **E. Florio:** None. **W. Junneng:** None. **F. Telese:** None.

Poster

083. Learning and Memory: Epigenetics

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 083.26/GGG10

Topic: H.01. Animal Cognition and Behavior

Title: Localization of nuclear receptor corepressor complex in the adult mouse brain

Authors: ***I. RUSU**, A. IEMOLO, P. MONTILLA-PEREZ, F. TELESE
Univ. of California San Diego, LA Jolla, CA

Abstract: Nuclear receptor corepressor 1 (NCoR1) and silencing mediator for retinoid or thyroid-hormone receptors (SMRT) are essential component of a multiprotein complex that mediates the repressive activity of nuclear receptors and other transcription factors. They associate with histone modifying enzymes that contain a catalytic domain able to catalyze the addition or removal of acetyl or methyl groups on histone proteins. Thus, the NCoR/SMRT complex actively silences target genes. During early brain development, NCoR and SMRT are expressed in neuronal stem cells and mediate transcriptional programs essential for neuronal differentiation. Recent findings suggest that the NCoR/SMRT complex is implicated in Reelin-dependent transcriptional pathways underlying memory formation. It is also known that NCoR complex binds to MeCP2, a protein mutated in Rett syndrome; and that loss of function of HDAC3 component of NCoR complex results in significant impairment of memory consolidation in mice. However, the role and the cell type specificity of this complex in adult brain have yet to be investigated. To address this question, we examined the distribution of NCoR and SMRT in the adult mouse brain. We performed immunohistochemistry analysis using coronal slices of brain tissue that were stained with primary antibodies for NCoR and SMRT. The antibodies used in these experiments were validated by western blot. Analysis of images obtained from fluorescence microscopy indicates that NCoR and SMRT are widely expressed throughout the brain with high level of expression in the pre-frontal cortex, striatum, dorsal and ventral hippocampus. As expected, the localization of NCoR and SMRT is confined in the nuclear compartment. To determine which neuronal or non-neuronal cell types of the adult brain express NCoR and SMRT, we are currently performing the co-staining of these proteins with several cell type-specific markers, including excitatory neurons, inhibitory neurons and glial cells (astrocytes, oligodendrocytes and microglia). Overall, our results suggest that NCoR and SMRT continue to be expressed in the adult brain and our analysis will define the cell-type

specificity of this complex, which will improve our understanding of their role in health and disease.

Disclosures: **I. Rusu:** None. **A. Iemolo:** None. **P. Montilla-Perez:** None. **F. Telese:** None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.01/GGG11

Topic: H.01. Animal Cognition and Behavior

Support: NIA Grant 5R01AG050598

Title: Olfactory function and insulin signalling in a rat model of T2DM and AD

Authors: ***K. Y. MANZI**, E. C. MCNAY
State Univ. of New York At Albany, Albany, NY

Abstract: Olfactory deficits are a common symptom of type II diabetes (T2DM) and Alzheimer's disease (AD). Both these pathologies are linked to insulin resistance in the brain, and T2DM is a major risk factor for subsequent AD. The olfactory bulb is a brain region that is known to be insulin-regulated, expressing both insulin receptors and the insulin-regulated glucose transporter GluT4. The olfactory deficits observed in T2DM and AD may therefore be due to insulin dysregulation in the olfactory bulbs, which are also the first brain region to show abnormal accumulation of beta-amyloid in animal models of AD. Olfactory impairment is an early marker of AD, and may thus be an indicator that T2DM is progressing towards AD. Obesity is a common cause of insulin resistance, and T2DM in human patients is commonly caused by lifestyle factors such as poor diet. In this study, we fed rats either a 'cafeteria' diet modeled after an obesogenic human diet, or a high-fat rodent chow, either of which commonly leads to obesity and insulin resistance; we then measured olfactory sensitivity over time. We developed a buried pellet test and olfactory discrimination task to measure olfaction. Surprisingly, the high-fat chow induced obesity, but not insulin resistance. The cafeteria diet group did not become obese but did have significantly larger fat pads than age-matched controls. However, unexpectedly, the groups did not differ on any of the behavioral tasks used; we made several discoveries with regard to procedure that may explain this and that will guide future work in this area. Animals from each group had samples taken from multiple brain regions, which were analyzed for molecular markers of insulin signaling, metabolism, and related pathways.

Disclosures: **K.Y. Manzi:** None. **E.C. McNay:** None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.02/GGG12

Topic: H.01. Animal Cognition and Behavior

Support: NIA Grant 5R01AG050598

Title: Molecular effectors of insulin's role in hippocampal memory processing across stages of memory

Authors: *G. S. FITZGERALD, L. P. MALLON, E. C. MCNAY
Behavioral Neurosci., Univ. At Albany, Albany, NY

Abstract: Our lab has previously shown that intrahippocampal insulin signaling is a critical component of hippocampal memory processing; we also showed that delivery of exogenous insulin to the hippocampus enhanced both memory and hippocampal glucose metabolism, whereas diet-induced insulin resistance impaired both. These data are consistent with the clinically-observed link between impaired central insulin signaling, often caused by type 2 diabetes, and development of Alzheimer's disease. Memory impairment associated with AD or T2DM is often primarily associated with deficits in encoding, rather than in retrieval. We have shown that the insulin-regulated glucose transporter GluT4 is likely a key player in transducing the impact of insulin on encoding. However, the impact of insulin on retrieval, and the mechanism(s) involved in such impact, remain to be determined. Preliminary data suggested that there may be distinct insulin-regulated processes involved in encoding vs. retrieval, possibly all downstream of a common insulin-receptor/Akt cascade. In this study we examined the effects of intrahippocampal insulin administration on three stages of memory processing: spatial working memory, as well as the encoding and retrieval of a contextual fear memory. We implanted microdialysis and microinjection cannulae into the left dorsal hippocampus of rats. After a recovery period, rats were tested in one of two memory tasks that are known to be hippocampally-mediated. Working memory was assessed by spontaneous alternation in the four-arm radial arm maze. Encoding and retrieval processes were assessed by freezing behavior in a contextual fear conditioning task. Prior to each test, rats received an intrahippocampal microinjection of either vehicle or insulin. To distinguish the contribution of insulin to memory encoding and retrieval processes, rats receiving contextual fear conditioning received microinjections before either the training or the testing phase, but not both. A microdialysis probe was used to track changes in hippocampal metabolism during spontaneous alternation testing. To investigate the molecular effectors of insulin's effects on the cognition, we dissected relevant brain regions (hippocampi, frontal cortex, hypothalamus, amygdalae) and used western blotting to measure the putative downstream targets of the insulin signaling cascade. Future work

will attempt to specifically modulate the identified downstream effectors of insulin, with the end goal of preserving healthy cognition even in a state of insulin resistance or deficiency.

Disclosures: G.S. Fitzgerald: None. L.P. Mallon: None. E.C. McNay: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.03/GGG13

Topic: H.01. Animal Cognition and Behavior

Support: 5R01AG050598

Title: Investigation of hippocampal insulin levels during a cognitively demanding task

Authors: *J. BATAILLE¹, S. DOUGLASS³, E. C. MCNAY²

²Behavioural Neurosci., ¹Univ. At Albany, Albany, NY; ³Psychology, SUNY Univ. At Albany, Mechanicville, NY

Abstract: Insulin is a key regulator of systemic glucose metabolism: it regulates glucose uptake from the blood and hepatic glycogen storage, for example. Additionally, insulin regulates brain metabolism and function: we have shown that intrahippocampal insulin signalling is a critical component of hippocampal memory processing, and that diet-induced insulin resistance extends to the brain where it impairs both cognition and glucose metabolism. Recent work from our lab has suggested that translocation of GluT4 is a key mediator of insulin's procognitive effects within the hippocampus.

Although insulin resistance is now well-established to occur within the CNS, and the balance of data suggests that at least some insulin is centrally derived, there are no data regarding insulin levels in the brain accompanying type 2 diabetes, nor during cognitive processing. Data are mixed with regard to measurements in the CSF, and opinions vary regarding the expected impact of systemic insulin resistance and hyperinsulinemia. Making such measurements *in vivo* is a technical challenge because of the relatively low levels of insulin and the high adhesion of the peptide to any sampling device. We used *in vivo* microdialysis and specially adapted methods to measure extracellular hippocampal insulin levels during a cognitive task. Male Sprague-Dawley rats were placed on either a control or diabetogenic, high-fat diet (HFD) for 13 weeks. The high fat diet consisted of high fat chow (60% fat and 20% fructose) together with 25% fructose in drinking water. Animals were then tested on a 20 minute spontaneous alternation task. Samples of perfusate were continuously taken prior to testing, during testing, and after testing. Somewhat surprisingly, animals showed no significant different in body weights between groups; however, HFD animals had significantly more fat and showed impaired glucose regulation when given a glucose tolerance test. Unexpectedly and contrary to our hypothesis, this impaired glucose

regulation was not accompanied by impairment on the alternation task. Additional key measures include both the perfusate insulin and post-mortem quantification of hippocampal insulin signaling and metabolism-related proteins.

Disclosures: J. Bataille: None. S. Douglass: None. E.C. McNay: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.04/GGG14

Topic: H.01. Animal Cognition and Behavior

Support: NIA grant 5R01AG050598

Title: Attenuation of the cognitive and physical effects of recurrent hypoglycemia by medium chain triglyceride administration

Authors: *S. DOUGLASS¹, G. C. TAPAWAN³, C. M. LEVINE³, E. C. MCNAY²
²Behavioural Neurosci., ¹Univ. At Albany, Albany, NY; ³Univ. at Albany, Albany, NY

Abstract: Recurrent hypoglycemia (RH) causes profound cognitive impairment and autonomic impairment in regulation of glucose during subsequent hypoglycemia. RH is typically caused by excess insulin in insulin-treated patients with diabetes. This pattern of insulin dysregulation induces further glucose dysregulation peripherally and within the CNS, including increased conservation of glucose reserves, thus exacerbating cognitive deficits during subsequent hypoglycemia. Medium chain triglycerides (MCT) can be used as an alternative fuel source by brain cells after transformation into ketones. We sought to examine whether providing this alternative fuel source could attenuate the impact of neuroglycopenia caused by RH. Medium chain triglycerides were administered i.p. to rats immediately prior to induction of hypoglycemia on each of three consecutive days. On the fourth day, animals were tested in a spontaneous alteration (spatial working memory) task with concurrent hippocampal microdialysis, followed by training on a contextual fear task, with retention testing a further 24h later. Post-mortem measurements included microdialysate glucose and lactate levels, and monocarboxylate/glucose transporters within the hippocampus and other brain regions. We hypothesize that MCT administration will attenuate the effects of RH: treated animals are expected to show neither cognitive changes nor adaptation in glucose/MCT transport. Our data will provide mechanistic insight into the clinically-demonstrated ability of MCT administration to protect against the deleterious effects of hypoglycemia.

Disclosures: S. Douglass: None. G.C. Tapawan: None. C.M. Levine: None. E.C. McNay: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

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Program #/Poster #: 084.05/GGG15

Topic: H.01. Animal Cognition and Behavior

Support: NIA grant 5R01AG050598

Title: Parsing the impact of zinc vs. insulin on hippocampal memory processing

Authors: *A. PICHE, S. DOUGLASS, G. M. OSTRANDER, E. C. MCNAY
State Univ. of New York at Albany, Albany, NY

Abstract: Insulin resistance is the defining symptom of type 2 diabetes and a key risk factor for Alzheimer's disease. We and others have shown that insulin is a key component of mechanisms that transduce hippocampal memory processing. In the hippocampus, insulin regulates glucose metabolism through translocation of the glucose transporter GluT4 and modulates several other molecular cascades.

Previous work has generally used a formulation that contains zinc to stabilize insulin. However, zinc itself modulates molecular signaling pathways including AKT and GSK3 β , which are both downstream of insulin. Zinc also regulates neuronal glutamate release, suggesting a potential further role in modulation of memory. Moreover, measurements of the electrophysiological impact of insulin has shown a marked difference between zinc-containing and zinc-free forms of insulin. Hence, delivery of zinc as an artifact of administering treatment to insulin-treated animals may confound studies of the impact of insulin on cognition and metabolism. This is especially true for studies using direct intrahippocampal administration, where zinc will be delivered to the hippocampus; in contrast, delivery of insulin from the pancreas would be unlikely to be accompanied by zinc because *in vivo*, the insulin hexamer, stabilized by zinc and calcium, breaks apart and releases the cations almost immediately after being released from pancreatic beta cells in the pancreas.

We therefore aimed to parse the separate effects of zinc and insulin on hippocampal metabolism and cognitive processes. Sprague-Dawley rats received a microinjection guide cannulae into their left hippocampus and were then treated with intrahippocampal delivery of Humulin (a zinc-containing insulin), Apidra (a zinc-free form of insulin), artificial extracellular fluid (aECF; a vehicle control), or zinc dissolved in aECF, prior to both (i) a 20 minute spontaneous alternation plus-maze task, followed by (ii) training on a novel object recognition task with retrieval testing 24h later. Brain samples from the left and right hippocampus along with the pre-frontal cortex were removed and analyzed for the presence of key proteins in the activation cascades via western blots. Evidence from current literature indicates a strong possibility that the impact of a zinc-insulin treatment may be due, at least in part, to the presence of zinc as opposed to insulin.

Disclosures: A. Piche: None. S. Douglass: None. G.M. Ostrander: None. E.C. McNay: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.06/GGG16

Topic: H.01. Animal Cognition and Behavior

Support: NIA Grant 5R01AG050598

Title: Estradiol treatment to attenuate the hippocampal impact of a high fat diabetogenic diet

Authors: *L. MAITNER, G. S. FITZGERALD, E. C. MCNAY
State Univ. of New York At Albany, Albany, NY

Abstract: Estradiol acts throughout the body; one key target that expresses large numbers of estradiol receptors is the brain, and specifically the hippocampus. Estradiol can exhibit neuroprotective effects in the brain. However, the set of pathways through which this occurs is not well understood. *In vitro* work has shown that administration of estradiol to hippocampal neurons inactivates caspase 3, a protease involved in apoptosis and the cleavage of tau. Cleavage of tau results in the formation of neurofibrillary tangles. Together with formation of amyloid-beta plaques, this is one of the hallmarks of Alzheimer's disease.

We tested the hypothesis that administration of estradiol to rats might attenuate the cognitive impairment caused by the ingestion of a high fat, diabetogenic diet whose long-term consumption causes insulin resistance and Alzheimer's disease pathologies. Administration of estradiol reversed the impairment on a novel object recognition task seen in high-fat animals, but unexpectedly did not ameliorate the impairment seen on a spatial working memory task.

In addition to behavioral measures, post-mortem analyses of hippocampal tissue measured molecular markers associated with estradiol signaling and memory formation. Ultimately, this study aims to elucidate mechanisms involved in a possible neuroprotective role for estradiol in individuals prone to cognitive dysfunction brought about by metabolic disease.

Disclosures: L. Maitner: None. G.S. Fitzgerald: None. E.C. McNay: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.07/GGG17

Topic: H.01. Animal Cognition and Behavior

Support: VA Grant I21 BX002085 (LPR)
VA Grant I01 BX001804 (LPR)
NIH R01AG050518 (JRF)
NSF Grant IOS-1656626 (CAG)

Title: Hippocampal-specific insulin resistance elicits dendritic atrophy of dentate gyrus granule neurons

Authors: *C. A. GRILLO^{1,2}, H. B. COWAN¹, V. A. MACHT¹, J. L. WOODRUFF¹, F. Z. LOYO-ROSADO¹, L. P. REAGAN^{1,2}

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Abstract: Insulin plays important roles in the central nervous system, including the hippocampus, which is associated with learning and memory. The high density of insulin receptors expressed in the hippocampus suggests that insulin promotes synaptic plasticity and cognitive function. Conversely, metabolic diseases such as diabetes and obesity are associated with insulin resistance that causes deleterious effects to the hippocampus. In our laboratory, we developed a lentivirus vector that selectively downregulates insulin receptors (LV-IRAS), which has allowed us to elicit insulin resistance in specific brain regions. Previously, we demonstrated that hippocampal-specific insulin resistance impairs spatial learning and synaptic plasticity in the absence of changes in body weight, body composition and peripheral glucose homeostasis. We therefore hypothesize that insulin has protective and neurotrophic effects on the hippocampus and that insulin resistance would have a deleterious effect on neuron morphology. Recently we reported that the specific knockdown of insulin receptor in the hippocampus resulted in decreases in the expression of immature neurons in the dentate gyrus and redistribution of pre- and postsynaptic markers in the cornu ammonis, without evidence of neurodegeneration. In view of these observations, the goal of the current study was to examine the effects of hippocampal-specific insulin resistance on hippocampal pyramidal neuron morphology by Golgi staining followed by a 3-D reconstruction. For this study we injected LV-IRAS in one side of the hippocampus while the contralateral hippocampus received the control virus, thus each rat served as its own control. The 3-D reconstructions showed simplification in the dendritic arborization of the superior and inferior blade of the dentate gyrus. More simply, hippocampal-specific insulin resistance elicits dendritic atrophy in the hippocampus. These results suggest that insulin resistance negatively impacts neuronal morphology plasticity, which may contribute to impairments in memory and hippocampal-dependent learning in metabolic disorders and in Alzheimer's disease.

Disclosures: C.A. Grillo: None. H.B. Cowan: None. V.A. Macht: None. J.L. Woodruff: None. F.Z. Loyo-Rosado: None. L.P. Reagan: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.08/DP12/GGG18

Topic: H.01. Animal Cognition and Behavior

Title: Supraphysiological levels of oxygen exposure during the neonatal period impairs signaling pathways required for learning and memory

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Abstract.Abstract1:

Background: Children born preterm, even with a relatively uncomplicated neonatal intensive care course, have reduced hippocampal volume and deficits in executive function and learning and memory compared to children born at term. In addition, preterm infants often require prolonged periods of supraphysiological levels of oxygen supplementation (hyperoxia) to maintain optimal oxygen saturation. We recently reported that adult mice who had prolonged hyperoxia exposure during their neonatal period (postnatal day [P]2 to 14) had spatial navigation memory deficits and associated with hippocampal shrinkage. However, the underlying cellular and molecular mechanisms for such hyperoxia-induced effects on memory pathways in adults are not known.

Objective: Using proteomic analysis, our objective was to determine the changes in receptors and signaling pathways necessary for long-term memory formation.

Design/Methods: C57BL/6 mouse pups were exposed to either 85% oxygen or air between P2 to 14. At P14, targeted analysis of hippocampal ligand-gated ion channels and proteins necessary for memory formation and bioinformatics analysis of differentially expressed hippocampal proteins were performed.

Results: Oxygen exposure decreased the amount of hippocampal mGLU7, TrkB, PI3K, AKT, ERK2, mTORC1, RPS6, and EIF4E (**Table 1**) and increased $\alpha 3$, $\alpha 5$, and Y2 subunits of GABA_A receptor and PTEN levels. Bioinformatic analysis of differentially expressed proteins indicated dysfunctions in mitochondria and global protein synthesis and translational processes.

Conclusion(s): Supraphysiological levels of oxygen exposure reduced proteins necessary for hippocampus-dependent memory formation and may adversely impact hippocampal mitochondrial function and global protein synthesis. These early hippocampal proteomic changes may account for memory deficits seen in preterm survivors following prolonged oxygen exposure.

Protein (Symbol)	Protein Log Fold Change in Hyperoxia Group	P value	Gene Expression Log Fold Change in Hyperoxia Group	P value
TrkB/ERK/PI3K Pathway				
Tropomyosin receptor kinase B (TrkB)	-1.09	0.04	-0.04	0.76
Protein kinase C α (PKCA)	+0.01	0.98	0.25	0.06
Protein kinase C β (PKCB)	+1.12	0.17	-0.27	0.009
Protein kinase C γ (PKCG)	-0.22	0.45	0.56	8.46E-07
Mitogen-activated protein kinase Kinase 1(MEK1)	-0.26	0.57	0.13	0.11
Mitogen-activated protein kinase Kinase 2(MEK2)	+0.53	0.35	-0.07	0.5
Extracellular signal-regulated kinase 1 (ERK1)	+0.58	0.36	0.18	0.12
Extracellular Signal-Regulated Kinase 2 (ERK2)	-1.33	0.02	0.15	0.03
Phosphoinositide 3-kinase (PIK3)	+0.25	0.13	-0.3	0.0007
Phosphatase and tensin homolog (PTEN)	+0.71	0.03	-0.63	3.66E-08
Protein kinase B (PKB-Akt3)	-1.02	0.02		1.81E-09
AKT interacting protein (AKTIP)	-1.27	0.03	-0.17	0.04
Mechanistic target of rapamycin (mTOR)	+0.50	0.48	-0.33	3.55E-05
Mechanistic target of rapamycin complex 1 (mTORC1)	-0.98	0.01	0.18	0.05
Ribosomal protein S6 RPS6	-0.89	0.04	0.20	0.04
Eukaryotic translation initiation factor 4e (EIF4E)	-1.18	0.008	0.15	0.05

Table 1: Effect of Hyperoxia on TrkB/ERK/PI3K Signaling Pathways (n=5 in Air group, 6 in Hyperoxia group, P=Hyperoxia vs. Air group)

Disclosures: M. Ramani: None. L.L. McMahon: None. A. Namasivayam: None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.09/GGG19

Topic: H.01. Animal Cognition and Behavior

Support: Association X-traordinaire, France

Title: Overcome the blood-brain barrier by the rational design of dodecyl creatine ester loaded nanoemulsion: A promising strategy for the treatment in creatine transporter disorder

Authors: *A. MABINDZO¹, G. ULLIO-GAMBOA², N. CAMUS¹, S. DÉZARD¹, A. KOKENGE³, A. PRUVOST¹, F. TARAN¹, M. SKELTON³

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Abstract: *Background.* The creatine (Cr) transporter (CrT) deficiency is an inherited metabolic disorder (CCDS1) characterized by cerebral Cr deficiency, which results in intellectual disability associated with epilepsy and autistic behaviour. CCDS1 affects about 1% of males with non-syndromic mental disability and is currently without a cure. We previously synthesized dodecyl creatine ester (DCE). This compound had proven to be effective in crossing the blood brain barrier (BBB) and to be internalized in primary neuronal cells. However, the low aqueous solubility and the degradation by plasma esterases limited its potential medicinal application. *Objectives.* We focus on the preclinical development of a new therapeutically approach based on the use of DCE incorporated into nanoemulsion (NE) to overcome the BBB. *Materials and methods.* The DCE-loaded NE was prepared by titration method. Size, polydispersity and zeta potential were analyzed by photon correlation spectroscopy. DCE encapsulation efficiency was quantified by validated LC-MS/MS and determined by the quotient of the no-encapsulated drug and the total drug content. Novel object recognition (NOR) tests were performed before and after mice treatment for ten days assessed in the ANY-box apparatus (Stoelting Company, Wood Dale, and IL). Performance was measured using ANY-maze® software. (a) DCE loaded NE (n = 12 [Slc6a8⁻/y]); (b) Vehicle (n = 12 [Slc6a8⁻/y]), and (c) (n=12 [Slc6a8⁺/y]). A discrimination index was calculated where the time spent observing the novel object was subtracted from the time spent observing the familiar object and then was divided by the total time of exploration. *Statistic.* Data were analyzed using one-way analysis of variance (ANOVA). *Results and discussion.* DCE-NE formed monodispersed populations (PDI≤0.2) with a mean size of around 150 nm and a positive charge surface. Due to its amphiphilic character, DCE was efficiently encapsulated into the optimized NE with an encapsulation efficiency of about 85%. Ten days of repeated DCE-NE nasal administration resulted in wider creatine brain distribution, evidenced by a significantly increase in Cr levels into the four different brain regions (cortex striatum

hippocampus and cerebellum) in all CCDS1 mice compare with the vehicle controls. Moreover, these mice had an enhancement in discrimination index for the novel object which results on learning and memory improvements related to the enhanced Cr brain content. *Conclusion.* We reported evidence about the feasibility of DCE encapsulation in optimized NE. DCE-loaded NE were effective to restores the cognitive function in CCDS1 mice attributable to targeting Cr in brain cells.

Disclosures: **A. Mabindzo:** None. **G. Ullio-Gamboa:** None. **N. Camus:** None. **S. Dézard:** None. **A. Kokenge:** None. **A. Pruvost:** None. **F. Taran:** None. **M. Skelton:** None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.10/GGG20

Topic: H.01. Animal Cognition and Behavior

Title: Effects of caffeine and adrenaline administration singly and in combination on memory and mGlutR1a in male Wistar rats

Authors: ***A. O. IMAMFULANI, B. V. OWOYELE**
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Abstract: Caffeine has been widely studied but it's effects on memory is still controversial. This study was therefore designed to investigate the effects of caffeine and adrenaline singly and in combination on memory in rats. Rats weighing about 140-200g were used for the study and were divided into three study groups with a common control group administered normal saline. Study groups 1; a,b,c, were administered 5, 10 and 15 mg/kg caffeine intraperitoneally (i.p), respectively for 6 weeks, study groups 2; a,b,c, were given 0.1, 0.2 and 0.3mg/kg adrenaline (i.p), respectively for 6 weeks, study groups 3; a,b,c, were administered 5mg/kg caffeine (i.p) + 0.1mg/kg adrenaline (i.p), 10mg/kg caffeine + 0.2mg/kg adrenaline (i.p) and 15mg/kg caffeine + 0.3mg/kg adrenaline (i.p) respectively for 6 weeks. After administration the rats were subjected to cognitive tests using Y-maze and Morris water maze. Immunohistochemistry was further conducted for mGlutR1a and GABA_A receptors in difference part of the brain. The result showed no significant difference in spatial memory in study groups 1 and study groups 2 (a,b) when compared to control while 2(c) showed significant ($p < 0.05$) decrease compared to control. Study groups 3: showed no significant difference in spatial memory when compared to control. Study groups 1 and 2 showed significant ($p < 0.05$) reduction in duration for the long and short term memory test when compared to control, while study groups 3 showed no significant difference compared to control. Caffeine and adrenaline also increased sensitivity of mGlutR1a in the hippocampus, amygdala and cerebral cortex of the rats. But it decreased GABA_A receptors in the hippocampus. It was therefore concluded that caffeine and adrenaline at the doses used in this

study either singly or in combination enhanced memory via activation of mGluR1a in the hippocampus.

Disclosures: **A.O. Imamfulani:** None. **B.V. Owoyele:** None.

Poster

084. Signal Pathways and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 084.11/GGG21

Topic: H.01. Animal Cognition and Behavior

Support: FONCICYT CONACYT 273553
UAM-PTC-585

Title: Glutamatergic deregulation in a metabolic syndrome murine model: Implications on NMDA receptors within lipid rafts and cognitive performance

Authors: ***K. R. GUZMAN-RAMOS**¹, **P. SALCEDO-TELLO**³, **E. S. GUTIÉRREZ-LÓPEZ**³, **S. HERNÁNDEZ-RAMÍREZ**², **L. AYALA-GUERRERO**^{3,2}, **M. VELASCO**³, **M. HIRIART**³, **F. BERMÚDEZ-RATTONI**³

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Abstract: Metabolic dysfunctions such as diabetes and metabolic syndrome are important health problems and represent risk factors for the development of mild cognitive impairment and dementia. However, it is still unclear how the chronic metabolic dysfunction leads, in some cases, to poor cognitive performance. One of the main neurotransmitter systems involved in synaptic plasticity and memory formation is the glutamatergic system through the NMDA receptors. Signal transduction after NMDA receptors activation is carried out efficiently within active synaptic sites such as lipid rafts, which are lipid membrane microdomains enriched in cholesterol and sphingolipids. It has been reported that lipid rafts composition is affected by high calorie diets, so it is possible that NMDA receptor subunits trafficking would be affected as well, producing the cognitive impairments induced by a high-sugar chronic diet. To test this hypothesis, we analyzed the constitutive GluN1 subunit of the NMDA receptor within lipid raft and non-lipid rafts fractions of dorsal hippocampus tissue from male Wistar rats exposed for 6 months to a 20% sucrose solution instead of drinking water and compared with same-age control rats. The high-sucrose diet induces increased adiposity, glucose intolerance, insulin resistance and dyslipidemia; constituting a well established model of metabolic syndrome. We also evaluated hippocampus-dependent memory tasks such as object location memory and Morris' water maze to compare cognitive function in animals treated with sucrose and untreated controls.

The results indicate a lower content of GluN1 protein, hence NMDA receptors, on the lipid rafts fraction of hippocampus from metabolic syndrome rats as well as low performance on the long-term memory tests of the spatial memory tasks. These could shed light on understanding the basic mechanisms that are linked to memory deficiencies related to high-calorie diets in terms of molecular changes that could affect the stability of memory traces.

Disclosures: **K.R. Guzman-Ramos:** None. **P. Salcedo-Tello:** None. **E.S. Gutiérrez-López:** None. **S. Hernández-Ramírez:** None. **L. Ayala-Guerrero:** None. **M. Velasco:** None. **M. Hiriart:** None. **F. Bermúdez-Rattoni:** None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.01/GGG22

Topic: H.02. Human Cognition and Behavior

Support: German Research Foundation (DFG; SFB/Transregio 169)

Title: Implicit acoustic sequence learning recruits the hippocampus

Authors: ***J. JABLONOWSKI**¹, P. TAESLER¹, Q. FU², M. ROSE¹

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Abstract: The exclusive role of the medial temporal lobe (MTL) for explicit memory has been questioned by several studies reporting MTL involvement during implicit learning. Previous studies showed that the involvement of hippocampus during implicit learning is not dependent on the level of consciousness but on the stimuli modality of the learnt material. It was hypothesized that the acquisition of implicit knowledge recruits the hippocampus in general if learning relates to the extraction of perceptual associations and not to motor responses related associations.

The aim of the current functional magnetic resonance imaging (fMRI) study was to examine whether activations within MTL structures are also found during implicit learning of auditory associations. Using a modified version of the classical serial reaction time task (SRT), participants were instructed to react to the presentation of five different tones. Unbeknownst to the participants, the tones followed an underlying sequential regularity, hence the acoustic sequence could be learned incidentally to form implicit memory. After training, the amount of implicit knowledge and possible explicit knowledge was estimated using a completion task, in combination with a confidence rating, a free-generation test and a post-experimental interview. These tests allowed us to measure participants' conscious state about the acquired knowledge

and to exclude participants revealing explicit knowledge. FMRI results provided evidence for the relation between hippocampus activation and implicit acoustic sequence learning. Hence, this study indicated a relation between hippocampal activation and memory formation of perceptual-based relational representation regardless of explicit knowledge. Based on our findings, we suggest a general functional role of the hippocampus for the formation of sequenced perceptual associations independent of the involvement of awareness.

Disclosures: **J. Jablonowski:** None. **P. Taesler:** None. **Q. Fu:** None. **M. Rose:** None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.02/GGG23

Topic: H.02. Human Cognition and Behavior

Support: Grant of Italian Ministry of Health for the project "Health Technology Assessment, usability and human factor for pediatric medical devices in neurorehabilitation"

Title: Human factors and cognitive ergonomics in pediatric robotic neurorehabilitation. A review of literature

Authors: ***S. ZAFFINA, JR.**, S. RONGONI, F. GILARDI, D. CASASANTA, F. DE FALCO, V. CAMISA, G. DALMASSO, M. VINCI
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Abstract: The introduction of new technologies and medical devices in health care needs a continuous assessment of the interaction with users, healthcare workers and patients. A specific field of research is focusing on the human factor and cognitive ergonomic (HFE) analysis about the successful application in clinical practice of man-machine models and new brain-machine interfaces. Aim of the study is to carry out a preliminary analysis of the research on HFE in pediatric robotic neurorehabilitation related to the starting phase of a project conducted in an Italian pediatric hospital. A literature research has been carried out on PubMed database. The key terms "Human factor" OR "Ergonomics" OR "Cognitive Ergonomics" AND "Pediatric" AND "Robotic" AND "Neurorehabilitation" AND "Review" were used to appropriately address the topic. A "lateral search" has also been performed to identify other relevant papers and documents (international reports, congress proceedings, etc.).

The analysis regarding studies and reviews on the topic shows a scarce number of papers. Most of the studies have been published in the last five years, witnessing the recent development of the robotic technologies in neurorehabilitation. The applications regard several pathologies, such as upper and lower limb rehabilitation, sensorimotor deficits, neurological gait disorders and

cerebral palsy. The majority of the studies selected are characterized by little samples and the use of games, sometimes in a virtual reality scenario, for their crucial role in the patient's motivation. The issue of human factor and cognitive ergonomic seems to be rarely treated by the researchers in the pediatric field. However, the research in robotic neurorehabilitation in adults shows several applications, especially in the stroke management. The past two decades have seen growing interest of rehabilitation interventions, based on the use of robotics. In spite of this fact and the acknowledgement of the importance of HFE-based healthcare system, the research on this topic appears at a beginning stage. Few therapy systems seem to have been evaluated in children and well-designed randomized controlled studies in this field are still lacking. A specific project is being carried out on the topic in an Italian pediatric hospital, with the collaboration and funding of the Italian Ministry of Health, coauthor of this study. Aim of the project is to evaluate the pediatric neurorehabilitation robotic devices, through the Health Technology Assessment approach, in the clinical efficacy, ergonomic compliance of the operators and patients, safety, technical characteristics, organization, social, ethic and legal aspects.

Disclosures: S. Zaffina: None. S. Rongoni: None. F. Gilardi: None. D. Casasanta: None. F. De Falco: None. V. Camisa: None. G. Dalmaso: None. M. Vinci: None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.03/GGG24

Topic: H.02. Human Cognition and Behavior

Support: NSFC 31421003

Title: Neural representations of object-based space information in the human medial temporal lobe and prefrontal cortex

Authors: *Z. BO¹, Y. NAYA^{1,2,3,4}

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Abstract: It is critical for the navigation in our daily life to perceive our self-location and retrieve a target-location. These two processes could both depend on the allocentric cognitive map, which is non-viewpoint dependent during the past-encoding of spatial information. In the present study, we examined how the two types of behavioral demands affect the representation patterns of spatial information in the medial temporal lobe (MTL) and its functionally-related brain areas. To do this, we devised a new 3-D spatial-memory task and measured BOLD signal (3T, Siemens) for 19 healthy subjects. In each trial, the subjects experienced as if they walked

toward three human characters using first-person perspective and stopped at the center of them. During the 6.0 second walking period, they were instructed to pay attention to detect the head movement of human characters rather than memorizing the positions of characters. During the 2.0 second facing period, they were faced with one of the human characters, and another character was presented as a target for 2.0 seconds in targeting period, each period was followed by a 2.0 second delay. The subjects indicated the direction of the target character relative to their self-position by pressing a button. Out of six different spatial patterns ('maps') defined by the positions of characters, three maps were randomly used for each subject. All subjects showed a high level of task accuracy during the scanning (mean accuracy = 94%, standard deviation = 0.01), and the post-scan interview showed that they did not notice the number of maps. In order to localize the relevant brain regions representing map information, we conducted represented similarity analysis (RSA) based on a general linear model, where each spatial information was specified by a binary regressor indicating "same" or "different" between each trial-pair in a similarity matrix. Our analysis revealed that 'maps' were represented in the middle hippocampus, which exhibited a significantly higher correlation of neural activity in map-same condition compared to map-different condition while subjects were faced with one human character ($P < 0.01$, voxel-wise threshold; $P < 0.05$, cluster-corrected). On the other hand, the medial prefrontal cortex (mPFC) encoded map information while subjects remembered the egocentric location information of a target character ($P < 0.01$, voxel-wise threshold; $P < 0.05$, cluster-corrected). These results suggest that both HPC and mPFC may carry the spatial information defined by the identities of multiple objects and their relative positions. However, the spatial information in these two brain areas may serve different functional roles.

Disclosures: Z. Bo: None. Y. Naya: None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.04/GGG25

Topic: H.02. Human Cognition and Behavior

Support: Hass Avocado Board Grant 70476

USDA National Institute of Food and Agriculture, Hatch project Grant 1009249

Title: Associations between dietary carotenoids and hippocampal-dependent relational memory

Authors: *C. N. CANNAVALE¹, K. M. HASSEVOORT², K. M. HORECKA³, C. G. EDWARDS³, S. V. THOMPSON³, H. D. HOLSCHEER³, N. J. COHEN³, N. A. KHAN¹

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Abstract: Dietary carotenoids, plant pigments with anti-oxidant properties, are known to accumulate in neural tissue. Although physiological carotenoid status has been linked to several domains of cognitive function, the relationship between habitual dietary carotenoid consumption and hippocampal-dependent relational memory is unknown. Additionally, it is currently unclear whether specific dietary carotenoids have differential impact on memory function. Accordingly, this study aimed to elucidate relationships between different dietary carotenoids and relational memory. We hypothesized that individuals with greater habitual consumption of carotenoids would exhibit superior performance during a relational memory task.

Adults aged 25-45 years old (N=149, 94 females) completed a spatial reconstruction (SR) task which involved reconstruction of 20 different arrays of 6 ambiguous figures. Task performance was evaluated based on accuracy of item placement during reconstruction, relative to the location of the item during the study phase. Diet was assessed using 7-day diet records and carotenoid intake was determined following analyses using the Nutrition Data Systems for Research (NDSR 2015). Specific carotenoids analyzed included lutein + zeaxanthin, β -carotene, and β -cryptoxanthin. Participants' intelligence quotient (IQ) and whole-body adiposity measures were determined using the Kaufman Brief Intelligence Test-2 and dual-energy X-ray absorptiometry, respectively. Hierarchical linear regression analyses were used to determine the relationship between dietary carotenoids and SR performance, while controlling for age, sex, whole-body percent fat, and IQ.

Dietary intake of all carotenoids analyzed were positively associated with performance on the SR task. Further, participants with higher carotenoid consumption were more likely to place items in their correct location (all model p 's <0.05) and less likely to place items in another's location (all model p 's <0.01). These relationships persisted even after adjusting for demographics, IQ, and adiposity as well as correcting for multiple comparisons.

Findings from this study were consistent with our *a priori* hypothesis that carotenoid consumption is positively associated with relational memory performance and indicates that carotenoids may play an important role in hippocampal function. However, further dietary interventions are necessary to determine whether increased carotenoid consumption improves hippocampal function.

Disclosures: C.N. Cannavale: None. K.M. Hassevoort: None. K.M. Horecka: None. C.G. Edwards: None. S.V. Thompson: None. H.D. Holscher: None. N.J. Cohen: None. N.A. Khan: None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.05/GGG26

Topic: H.02. Human Cognition and Behavior

Support: René and Susanne Braginsky Foundation (KES)
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Title: Dynamic causal modeling of repetition suppression of visual ERPs to unattended objects

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Abstract: Repetition suppression (RS) refers to the decrease in neural responses to repeated relative to novel stimuli and is thought to reflect plasticity mediating perceptual learning. Although RS has been widely studied, the network dynamics underlying RS for visual stimuli are not well understood. Here we used dynamic causal modelling (DCM), a spatiotemporal generative modeling framework for event-related responses (ERPs), to explore networks of brain areas that may mediate RS during automatic processing of objects. We used a roving paradigm to elicit ERPs to black and white drawings of common objects in healthy volunteers (n=17). First, we used a set of models to identify the architecture of the most likely network including occipital, fusiform, and frontal sources. We used Bayesian model comparison to select the most plausible network. Second, we tested further variants of the winning model to investigate which connections most likely conveyed plasticity during RS. These models incorporated the hypotheses that differences in ERPs to the first and sixth presentation of physically identical stimuli were caused by changes in 1) forward, 2) backward, and 3) forward and backward connectivity between sources. Furthermore, each model had a variant where modulation of within-source local gain was allowed to contribute to RS effects. Bayesian model comparison showed that, with a protected exceedance probability >94%, the most likely model incorporated plastic changes in forward and backward connectivity between occipital, fusiform and frontal sources bilaterally, as well as changes in local gain (adaptation) at occipital sources. To our knowledge, this initial analysis represents the first attempt to establish network models of neuronal plasticity underlying RS during automatic object processing and infer the model's parameters from measured ERPs. Consistent with predictive coding, our results indicate that dynamic changes in connectivity take place in a hierarchical network during RS of visual ERPs.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.06/GGG27

Topic: H.02. Human Cognition and Behavior

Title: The bright side of training in the dark: Audio-visual spatial recalibration in firefighters

Authors: *I. TISSIERES¹, G. LOQUET³, J. ANKEN², C. WINDLER¹, S. CLARKE¹, S. CROTTAZ-HERBETTE¹

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Abstract: Auditory spatial abilities are very plastic and sensitive to visual influences. In the past decades, various studies showed improved sound localization following visual deprivation illustrating how cross-modal plasticity modulates auditory spatial attention to compensate visual deficits and maintain reliable spatial navigation. Firefighters are trained to work and navigate in stressful conditions with very limited visual inputs. During interventions, they have to rapidly identify and localize dangers while staying attentive to any human sound emanating from the surrounding noise. With the hypothesis that the recurrent limited vision induced changes in firefighters' auditory spatial abilities, we investigated auditory spatial perception as well as visuo-spatial and non-lateralized attentional capacities in 93 participants (24 controls, 28 volunteer firefighters and 41 professional firefighters). Furthermore, we hypothesized that firefighters' expertise would be specific to meaningful sound objects and would rely therefore on the lateral 'Integration' pathway, an auditory pathway integrating both position-independent and position-linked representations. Auditory spatial perception was evaluated in the azimuth, with a free-field set-up including nine sound positions ranging from -80° to 80°. Stimuli were either meaningless sounds (broadband noises) or sound objects (environmental sounds) and were presented either alone, or with sound distractors. To analyze firefighters' spatial expertise, the effect of sounds' semantic content and the effect of sound distractors, mixed-design ANOVAs were performed. Firefighters, compared to controls, showed an enhanced performance at localizing peripheral sounds and a reduced performance at localizing central sounds. Moreover, professional firefighters showed fewer errors for sound objects whereas control participants showed fewer errors for meaningless sounds. In addition, firefighters showed consistent expertise for peripheral sound positions and reduced performance for central sound positions when sound distractors were added. Finally, visuo-spatial and non-lateralized attentional performances were similar for the three groups. Our findings show that a specific training can lead to an auditory spatial expertise. Moreover, the dissociation in localization performances between sound types reveals that firefighters have a particular expertise in localizing sound objects. This expertise might rely on a specific neural pathway integrating both sound identity

and sound location information, that would be distinct from the *What* and *Where* auditory processing streams.

Disclosures: **I. Tissieres:** None. **G. Loquet:** None. **J. Anken:** None. **C. Windler:** None. **S. Clarke:** None. **S. Crottaz-Herbette:** None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.07/HHH1

Topic: H.02. Human Cognition and Behavior

Support: NIH R21 AG056145

Title: Spatial exploration through the world of Minecraft leads to improvements in hippocampus associated behaviors

Authors: ***C. M. HENNINGFIELD**¹, **G. D. CLEMENSON**², **C. E. STARK**²

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Abstract: Exposing animals to a larger and more stimulating environment can have a positive impact on both the structure and function of the hippocampus. While these enriched environments are comprised of multiple elements, the spatial exploration that occurs when exposed to a novel environment, has been singled out as a critical component. We previously showed that playing video games that center around 3D environments are capable of improving performance on a hippocampus-associated task, suggesting that some video games may act as a human correlate of environmental enrichment. While the results of this study are in line with the idea that spatial exploration is important for the beneficial effects of 3D video games, another plausible hypothesis is that simply learning something novel is important. Here, we use the open-world video game Minecraft to isolate and test two different components of video games: Exploration and Complexity. When compared to an internal Minecraft control group, our results suggest that while spatial exploration is highly correlated with improvements in hippocampus behavior, complexity can make a significant contribution to improvements in performance. Data presented here demonstrate that performance on hippocampus-associated behavior can be modulated by simply altering the experience of an individual within the world of Minecraft.

Disclosures: **C.M. Henningfield:** None. **G.D. Clemenson:** None. **C.E. Stark:** None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.08/HHH2

Topic: H.02. Human Cognition and Behavior

Support: NIH R21 AG056145

Title: Exploring the transfer of spatial information in a virtual representation of a real world environment

Authors: *G. D. CLEMENSON, C. E. STARK
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Abstract: It is well accepted that the hippocampus is important for spatial memory and navigation. We previously showed that playing 3D video games can improve performance on hippocampal cognition suggesting that the hippocampus may also play a role in the spatial navigation and memory of video game environments. While the hippocampus may be active during the navigation of real and virtual space, there are clear differences in the way that we experience each of these environments. Here we present a series of experiments that are designed to explore the behavioral relationship between real environments and virtual environments. We create virtual representations of two real-world locations on the UC Irvine campus to understand if spatial information transfers from one environment to the other and more specifically, address the type of information that transfers. In addition, we use a virtual version of the T-Maze task to address the differences in spatial strategies used when navigating a virtual environment on a flat computer screen versus the real world. Results from these experiments show that spatial information about location does transfer between real and virtual environments, however, navigating on a 2D computer screen can influence the type of strategy used.

Disclosures: G.D. Clemenson: None. C.E. Stark: None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.09/HHH3

Topic: H.02. Human Cognition and Behavior

Support: NIMH R01MH069456
NSERC PDF (JDW)

Title: Impact of representational overlap on learning-induced representational change

Authors: ***J. D. WAMMES**¹, K. A. NORMAN², N. B. TURK-BROWNE¹

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Abstract: Successful behavior requires that we constantly update the representational structure of memory to encode the statistics of our environment. As a simple form of such learning, prior work has shown that when incoming stimuli repeatedly co-occur in time, their neural representations tend to become more overlapping, especially in hippocampus. This work also revealed an unexpected exception to this pattern: when the co-occurring stimuli had a pre-existing relationship, due to visual similarity, their hippocampal representations became less similar as a result of learning (Schapiro et al., 2012). Here we were interested in further exploring the idea that regularities can induce representational change between items, but that the nature of the change (i.e., whether integration or differentiation occurs in memory) depends on the baseline overlap of the item representations. Pairs of images were synthesized using a convolutional neural network (CNN), pre-trained for object recognition, such that they spanned a continuum of visual similarity, as measured by RSA across high-layer CNN features. To validate this model-generated similarity continuum, subjective ratings were collected from 30 human participants completing a 2D arrangement task, in which they placed the images such that the pairwise distances corresponded to their perception of visual similarity. Critically, there was high correspondence between the RDM derived from CNN features, and an RDM that was derived empirically from participants' subjective distance ratings. We sampled 8 image pairs from this visual similarity space and embedded them in a statistical learning paradigm, to obtain a behavioral measure of representational change. Before and after learning, participants completed a numerosity judgment task, in which they had to indicate which of two images appeared more often in a rapid stream of images. Importantly, one of the test images was from a pair, whose pairmate also appeared in the stream. We predicted that memory integration would increase bias toward selecting the test image from the pair, as the two members of the pair would become more confusable. Conversely, differentiation would lead to a decreased bias toward the target pair. Pre-existing visual similarity/overlap between pairmates affected the bias, with the integration pattern occurring in the mid-range of similarity, and differentiation occurring at higher levels of similarity. We are now conducting a high-resolution fMRI study to relate these behavioral findings to pre-post changes in neural representations, both in the hippocampus and in visual areas encoding the features exploited by the CNN to generate the images.

Disclosures: **J.D. Wammes:** None. **K.A. Norman:** None. **N.B. Turk-Browne:** None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.10/HHH4

Topic: H.02. Human Cognition and Behavior

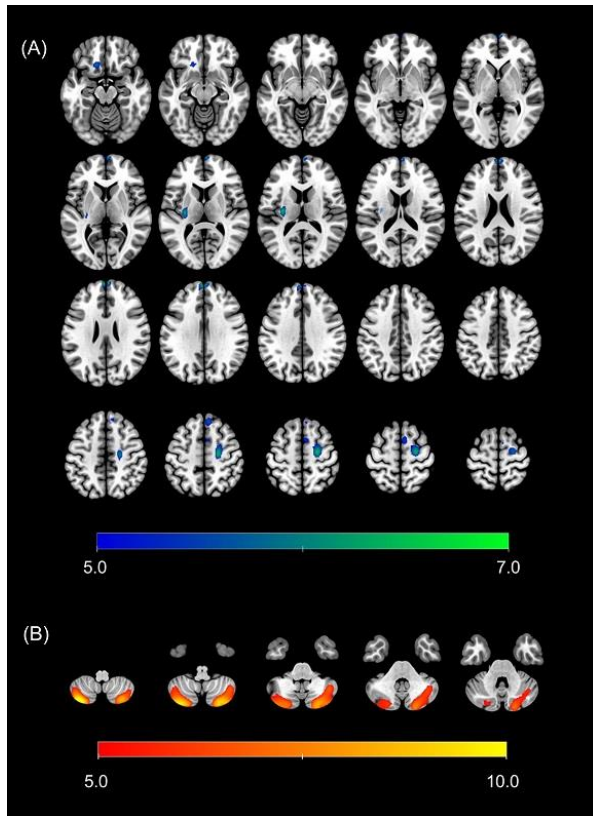
Support: NRF-2015M3C7A1064832

Title: Brain perfusion abnormalities in patients with persistent postural-perceptual dizziness

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Abstract: Persistent postural-perceptual dizziness (PPPD) is a recently defined syndrome characterized by persistent dizziness, unsteadiness, and/or non-spinning vertigo interrupting daily life. PPPD is the most common cause of vestibular syndrome in middle-aged patients. While it has been suggested that high level of anxiety and functional changes in postural control strategy and multi-sensory information processing and integration may be underlying the pathophysiology, its neural mechanisms are poorly understood. The aim of the study was to examine regional cerebral blood flow (rCBF) in patients with PPPD using single photon emission computed tomography (SPECT). A total of 25 patients with PPPD (mean age, 61 ± 18.9 ; 21 women) and 25 healthy controls (mean age, 56 ± 14.0 ; 20 women) participated in the study. All participants underwent ^{99m}Tc-HMPAO SPECT brain scans and the patients completed the Dizziness Handicap Inventory (DHI). SPECT images were compared between the groups using statistical parametric mapping. Correlational analysis was performed to assess the relationship between rCBF and dizziness severity. Among the patients, the mean duration of the disease was 35.4 ± 48.6 months and the mean DHI score was 54.4 ± 20.0 . No significant difference was found in age and gender between the groups. Compared with controls, PPPD patients showed a significantly decreased rCBF in the insula and frontal lobe, mainly in the left posterior insula, bilateral superior frontal gyrus, right inferior frontal gyrus, right precentral gyrus, and left medial orbital gyrus ($p < 0.05$, FWE-corrected; Fig 1). Moreover, PPPD patients showed a significant rCBF increase in the bilateral cerebellum compared with controls ($p < 0.05$, FWE-corrected; Fig 1). No significant correlation was found between the DHI score and the rCBF in both the decreased ($p = 0.57$) and increased regions ($p = 0.32$) of the patients. In conclusion, patients with PPPD revealed insula and frontal hypoperfusion and cerebellar hyperperfusion compared with controls. Our findings are consistent with results from previous neuroimaging studies.



Disclosures: J. Im: None. S. Na: None. H.S. Jeong: None. Y. Chung: None. I. Song: None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.11/HHH5

Topic: H.02. Human Cognition and Behavior

Support: Center for Computation and Technology at LSU

Title: Strengthening spatial reasoning: Elucidating the neural mechanisms associated with mental rotation skill development

Authors: *K. MOEN¹, S. M. SALTZMANN¹, L. M. BURLEIGH¹, L. G. BUTLER², J. RAMANUJAM³, A. S. COHEN¹, M. R. BECK¹, S. G. GREENING¹
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Abstract: STEM careers heavily rely on spatial reasoning skills (e.g., mental rotation). Previous research suggests that spatial reasoning skills improve with training (Meneghetti et al., 2017). However, the impact of spatial reasoning training on the neural mechanisms of mental rotation is

less understood. We investigated how brain activation changed as the result of mental rotation training. Specifically, we were interested in the visuospatial network, including the inferior and superior parietal lobes, and the premotor cortices (Logie et al., 2011), and the default mode network. The current study sought to improve spatial reasoning skills of introduction to chemistry students, and elucidate the neural mechanisms involved in mental rotation improvement pre- and post-training. First, participants completed a behavioral mental rotation task with three-dimensional cubes. Second, participants completed a modified version of the same mental rotation task in an fMRI scanner. The fMRI task utilized a block-design, two stimuli were presented side-by-side and participants responded if the two stimuli were rotated versions of the same item or were mirror versions of each other. Participants completed 30-second blocks in which the images that were either not rotated (control blocks), or were rotated 60°, 100°, or 140° (rotation blocks) from each other. After the first two pre-training sessions, participants were matched by sex, age, GPA, and pre-training accuracy, and were assigned to either the experimental training condition or the control training condition. The experimental training was identical to the pre-training behavioral task. The control training was a numerical estimation task. Participants saw two random dot arrays per trial and responded whether the two arrays contained the same or different number of dots. After six training sessions over three weeks, participants completed the same behavioral and neuroimaging tasks from pre-training. Replicating previous research for behavioral data, mental rotation response time increased and accuracy decreased as angular disparity increased. Accuracy increased from pre- to post-training for both training groups, but the increase was significantly larger for the experimental training group. Rotation blocks were associated with activation in the visuospatial network, whereas control blocks led to activation in the default mode network. Furthermore, increased activation in the default mode network during the pre-training rotation blocks was associated with higher improvement in accuracy from pre- to post-training. Further differences between pre- and post-training will be discussed.

Disclosures: **K. Moen:** None. **S.M. Saltzmann:** None. **L.M. Burleigh:** None. **L.G. Butler:** None. **J. Ramanujam:** None. **A.S. Cohen:** None. **M.R. Beck:** None. **S.G. Greening:** None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.12/HHH6

Topic: H.02. Human Cognition and Behavior

Support: NIH R01EY019466

NSF BCS 1539717

NSF 1632738

Title: Transfer of tactile perceptual learning scales with the spatial resolution of untrained sensory receptors

Authors: *S. M. FRANK^{1,2}, A. H. OTTO², L. FORSTER², K. HENSE², Y. SASAKI¹, P. U. TSE³, M. W. GREENLEE², T. WATANABE¹

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Abstract: Our sensory systems are highly plastic and subject to change depending on our perceptual experiences. For example, systematic training can lead to improved perception, referred to as perceptual learning (PL). How specificity and transfer of PL occurs is a fundamentally important question, because it provides information about the mechanisms of plasticity and extent of the plasticity in the brain underlying PL. Despite such importance, rules of transfer of PL are little known. For example, for tactile PL, transfer of learning has been reported for untrained body parts but factors determining the amount of transfer have remained unclear. Here, we show a general rule of transfer. A greater amount of transfer occurs from a body part with coarser spatial resolution to another part with finer spatial resolution. A stimulation device was constructed that presented tactile moving patterns to the surface of the body. Blindfolded participants were trained to detect a target pattern among distractor patterns in a tactile search paradigm. Three groups of right handed and right footed participants trained either on the surface of the right palm, the right foot sole, or the right cheek, respectively. The spatial tactile resolution was highest for the palm (mean 2-point thresholds = 11 mm), slightly lower for the cheek (13 mm), and lowest for the foot sole (20 mm). We found that differential transfer effects of learning scaled with the spatial resolution of the untrained receptors and also obtained this result when we controlled for greater learning difficulty at body parts with lower spatial resolution. Specifically, we observed transfer of learning from the trained foot to the untrained hands and, to a slightly lesser extent, to the untrained cheek. Moreover, learning transfer from the trained cheek to the untrained hands was greater than to the untrained feet. Finally, there was only partial transfer of learning from the trained hands to the untrained cheek and feet, whereby greater transfer was observed to the cheek than to the feet. These results show that transfer occurs from a body part with a lower spatial resolution to that with a higher resolution. One possible explanation is that the connectivity between sensory representations of different body parts and higher-order cortical areas scales with the spatial resolution of the receptors. That is, higher-order areas could have stronger connectivity with sensory representations of high-resolution body parts such as the hand or cheek than with low-resolution body parts such as the foot. Therefore, transfer of learning would be expected from the foot to the untrained hand and cheek, but not for the opposite direction.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.13/HHH7

Topic: H.02. Human Cognition and Behavior

Title: Transcranial direct current stimulation and tonal perception in musicians and non-musicians

Authors: *E. SOTO¹, R. VEGA², C. ROMERO²

¹Benemerita Univ. Autonoma de Puebla, Puebla Pue, Mexico; ²Inst. de Fisiología, Benemerita Univ. Autonoma de Puebla, Puebla, Mexico

Abstract: The use of transcranial direct current stimulation (tDCS) has increased in recent years, since it modulates cortical activity. tDCS is considered as a technique of neuromodulation, because it modifies the neural excitability due to changes in electrical gradients causing the membrane potential to change and affecting the action potential discharge probability as well as neurotransmitters release of neurons in the cortex. It is reported that certain configuration of electrodes in specific areas of the head can improve learning processes. The tDCS is safe, and it has been shown that anodic stimulation improves performance in various motor tasks. In the laboratory we were interested in determining its influence on auditory (musical) perception, which is why we have focused on using tDCS during a tuning test. For the experiments 69 voluntary subjects with mean age of 23 ± 2.73 years, and consent informed according to the Helsinki declaration of Ethical Principles for Medical Research Involving Human Subjects. An experimental problem group was exposed to tDCS in the temporal region (electrodes in T3-Fp2 or T4-Fp1, 1 mA, 10 min, using a Soterix 1x1 device) and control group were exposed to false tDCS. Additionally, the population was divided into a group of musicians (music students and professionals) and subjects without music studies. The error and latency between groups to identify three tones: La in 3rd octave (220 Hz), Fa in 6th octave (1397 Hz) and Re in 9th octave (9397 Hz) was compared. The tones were produced by a wave generator and subject respond using another wave generator, and the difference was measured and percent error calculated. In subjects without musical training, the left anodic stimulation ($n = 9$), and the right cathodic stimulation ($n = 8$) make the detection of the tones significantly more accurate, whereas in subjects with music studies ($n = 25$) there were no significant differences in the accuracy of the responses with the tDCS. The response latency was greater in all the groups with cathodic stimulation. The results indicate that the tDCS in the temporal regions positively modulates the tone detection but retards its execution and the anodic stimulation improves the execution of the tuning task.

Disclosures: E. Soto: None. R. Vega: None. C. Romero: None.

Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.14/HHH8

Topic: H.02. Human Cognition and Behavior

Support: NIH R01EY019466

Ruhr University Bochum Research School PLUS (DFG GSC 98/3)

Title: LTP-like visual stimulation elicits task-dependent changes in the perception of orientation

Authors: *A. MARZOLL, I. CHAVVA, T. WATANABE

Dept. of Cognitive, Linguistic, and Psychological Sci., Brown Univ., Providence, RI

Abstract: Previous work has shown that if a stimulus is intermittently flickered at a relatively high temporal frequency, it facilitates perceptual learning of orientation discrimination ability (Marzoll, Saygi & Dinse, *in preparation*). Thus, this stimulation was termed LTP-like stimulation. However, its underlying mechanism has yet to be clarified. Perceptual learning could result from sharpening tuning curves of orientations surrounding the trained orientation (Schoups et al., 2001; Yang & Maunsell, 2004) and/or reduced correlated variability in populations of sensory neurons (Ni et al., 2018; Doshier & Lu, 1998). If LTP-like stimulation leads to a sharpening of tuning properties, it should cause no change or decrease in performance in an orientation detection task, which may be based on the peak of tuning properties of the trained orientation. To determine which is more likely, we investigated how performance of human observers is changed by LTP-like stimulation in an orientation detection task. Seven subjects practiced in a two-interval forced choice detection task of oriented Gabors for eight days prior to visual stimulation. On the ninth day, detection performance was compared before and after 60 min of exposure to LTP-like stimulation with a Gabor that was intermittently flickered at an intra-train frequency of 10 Hz for 1 s, with 5 s in between trains. 90 min after stimulation, the average signal-to-noise thresholds for the orientation of the stimulated Gabor were significantly increased by 83.7% and for the orthogonal control orientation by 77.4%. The impairment persisted for at least 3 h after offset of LTP-like stimulation. On the following day, performance did not differ from pre-stimulation levels for both. Together with our previous finding, LTP-like stimulation appears to exhibit either facilitatory or impairing effects depending on the exact nature of the task. This suggests that LTP-like stimulation changes orientation tuning properties that may cause different results for detection and discrimination training and not noise variability reduction that may increase performance on both detection and discrimination tasks.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.15/HHH9

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 AG046646
ONR Grant N000141612829

Title: Temporal alignment of cortical slow oscillations with heart rate bursts during sleep predicts perceptual performance

Authors: *M. NAJI¹, G. P. KRISHNAN¹, E. A. MCDEVITT², M. BAZHENOV¹, S. C. MEDNICK³

¹Dept. of Med., UC San Diego, La Jolla, CA; ²Princeton Neurosci. Inst., Princeton, NJ; ³Dept. of Cognitive Sci., Univ. of California, Irvine, Irvine, CA

Abstract: Central and autonomic nervous system activity are coupled during sleep. Cortical slow oscillations (SOs, <1Hz) coincide with bursts in heart rate (HR), but the functional involvement of this coupling in cognition remains elusive. In this study, we examined the association between SO-HR timing during three sleep episodes with perceptual performance and sleep-dependent learning on a perceptual learning task. Subjects (n=40) took polysomnographically-recorded naps at 1:30-3:30PM during three in-lab study days, spaced two weeks apart. On each in-lab day, subjects were tested on a texture discrimination task (TDT) at 9AM and 5PM. For each visit, we detected SOs in Stage 2 sleep. We then analyzed HR within the 5 second window following the SO downstate. The SO-HR timing was measured as the temporal delay between the trough of the SO down-state and peak of the HR acceleration. We found that detected SOs during stable Stage 2 bins co-occurred with a peak in HR, which was 12.09 ± 1.48 % significantly above the average Stage 2 heart rate ($p=.0004$). A Pearson correlation revealed that SO-HR time intervals were correlated with TDT performance in both pre- (visit 1: $r=0.46$, $p=.004$; visit 2: $r=0.38$, $p=.033$; visit 3: $r=0.58$, $p=.002$) and post-nap sessions (visit 1: $r=0.49$, $p=.002$; visit 2: $r=0.45$, $p=.010$; visit 3: $r=0.52$, $p=.008$). Surprisingly, there was no significant relation between SO-HR intervals and TDT performance change in any visit (visit 1: $r=0.09$, $p=.598$; visit 2: $r=0.01$, $p=.975$; visit 3: $r=-0.12$, $p=.561$). To conclude, we found that shorter SO-HR intervals were associated with faster perceptual processing speed. This was the case for both pre- and post-nap sessions on three separate study visits. We hypothesize that our novel measure of SO-HR timing during sleep could reflect a general marker of CNS/ANS communication speed that may be related to perceptual speed.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.16/HHH10

Topic: H.02. Human Cognition and Behavior

Support: James S. McDonnell Foundation

Title: Direct comparison of rats, humans and reinforcement learning agents reveals evidence of predictive maps to navigate stochastic environments

Authors: ***W. J. DE CO THI**¹, **E. GRIESBAUER**², **C. LACAUX**³, **L. FLETCHER**², **C. NEWTON**⁴, **R. GRIEVES**², **E. DUVELLE**², **S. RENAUDINEAU**², **D. A. BENDOR**², **R. SILVA**², **C. BARRY**⁵, **H. J. SPIERS**²

¹CoMPLEX, ²Univ. Col. London, London, United Kingdom; ³Brain and Spine Inst., Paris, France; ⁴Univ. of Cambridge, Cambridge, United Kingdom; ⁵UCL, London, United Kingdom

Abstract: The mammalian brain has developed a remarkable capacity to flexibly navigate dynamic environments, exploiting shortcuts and taking efficient detours when needed. Past research has focused on three generally separate approaches: studying rats in mazes, humans in virtual reality and reinforcement learning (RL) algorithms in simulated worlds. Here we present a novel experimental framework allowing direct comparison between rats, humans, and artificial RL agents as they navigate to a hidden goal in an open arena while negotiating dynamically shifting canyons that obstruct movement. Initial analysis reveals that rats and humans display many similarities in their behaviour: demonstrating an impressive ability to adapt to blocked paths and also common errors involving failures to suppress previously rewarded routes that are no longer effective. Equally the trajectories of both species are most similar to the simulated trajectories of RL agents employing a successor representation their environment, providing support for the view that the neural systems for navigation use a predictive map of the environment to facilitate flexible behaviour.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.17/HHH11

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1634157
APDA Center Pilot Grant

Title: Implicit learning of bayesian priors in a perceptual decision-making task

Authors: ***B. J. KNOWLTON**¹, V. THAKUR¹, A. PERUGINI², M. A. BASSO³
¹Psychology, ²Psychiatry and Biobehavioral Sci., ³Psychiatry and Biobehavioral Sci. and Neurobio., UCLA, Los Angeles, CA

Abstract: Accumulation of sensory evidence is an essential part of perceptual decision-making. In addition, previous experience can lead to biases in decision-making, i.e., subjects use Bayesian priors to influence decisions. In this study, we assessed whether these priors could be learned implicitly and thus could influence decision-making without awareness. Subjects were asked to choose whether a visual stimulus presented on a screen, a dynamic Glass pattern (Glass, 1969), appeared oriented leftward or rightward. The coherence of the orientation signal varied across the stimuli, making the decision more or less difficult on each trial (Perugini et al., 2016, 2018). Additionally, the Glass patterns appeared in one of two colors. One group was given patterns in both colors with equal orientation priors (50% left, 50% right), and the second group was given patterns with unequal direction priors (e.g. one color 80% left, 20% right, and the other color 40% left and 60% right). After testing, subjects were asked about whether or not they noticed if there were any differences in the likelihood of the orientation for either of the colors. The orientation prior and Glass pattern color were counterbalanced across participants. Two main parameters were calculated from the behavioral choice data: the bias and slope at the zero coherence condition for both the colors. We found that participants in the first group showed no bias for one side or the other for the zero coherence condition. While the second group reported no explicit knowledge of a tendency for the patterns to occur in one orientation vs. another, the bias for this group at zero coherence was the sum of the priors for the two colors (significantly different from 50%, $p < .05$). Thus, implicit learning about Bayesian priors was not specific to the color, but was accrued across all stimuli in the task. These results suggest that perceptual decision-making can be influenced by implicitly learned priors, yet this learning may lack specificity and appears to generalize across stimulus types.

Disclosures: **B.J. Knowlton:** None. **V. Thakur:** None. **A. Perugini:** None. **M.A. Basso:** None.

Poster

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Program #/Poster #: 085.18/HHH12

Topic: H.02. Human Cognition and Behavior

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Title: Learning predictive temporal structure under uncertainty

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Abstract: Experience is thought to facilitate our ability to extract structures from streams of events. We have shown that extracting complex temporal regularities relates to individual decision strategy (matching vs maximization). Here we test whether this ability for learning predictive structures is maintained under uncertainty and whether it generalizes. In particular, we trained participants with sequences of symbols determined by first-order Markov models. Participants were asked to indicate whether a test symbol that was presented following each sequence matched their expectation based on the preceding sequence. We manipulated ‘uncertainty’ in the sequences in three respects: probability of symbol occurrence, stimulus presentation rate and feedback. Our results demonstrate that: (1) Probability of occurrence is important for structure learning; similar probabilities of symbol occurrence compromised performance on the prediction task. (2) Increasing uncertainty in stimulus presentation rate by temporal jittering did not impair participants’ performance, but led participants to adopt a strategy closer to probability maximization. (3) Feedback played an important role in predictive learning: Trial-by-trial feedback yielded a larger improvement of performance than block feedback or no feedback, and encouraged participants to adopt a strategy closer to maximization. Providing uncorrelated feedback resulted in limited improvement. Further, we investigated whether learning transfers from familiar symbols to novel ones. After training, participants were tested with a new sequence of stimuli which comprised four different symbols. It was shown that predictive learning of temporal statistics transferred fully to distinct new stimuli. Correlating individual strategies with learning and transfer performance showed that observers that adopted the maximization strategy showed improved performance and higher learning transfer. Taken together, our results suggest that adopting maximization reduces uncertainty when learning in variable environments. Further, maximization facilitates predictive learning and generalization.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.19/HHH13

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant - 436140-2013

Title: Spatial learners display decreased risk taking behavior in the Iowa Gambling Task

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Abstract: The current study investigated whether different navigation strategies are associated with differences in risk taking behavior as measured by the Iowa Gambling Task (IGT). Neuroimaging studies of healthy young adults and lesion studies of non-human species show that navigation can be achieved using two different strategies that depend on separate brain systems. The *spatial strategy* involves building relationships between landmarks in an environment to create a cognitive map and is dependent on the integral function of the hippocampus. The *response strategy*, in contrast, entails learning a series of movements (e.g., left and right turns) from given positions that act as stimuli and is dependent on the integrity of the caudate nucleus (CN). The CN is also a structure centrally implicated in the brain's reward circuit. We measured 50 participants' navigation strategies (response vs. spatial), using the 4-on-8 virtual maze (4/8VM) and also tested them on the IGT. Previous results using the 4/8VM have shown that response learners, who display more grey matter and functional activity in the CN, have higher rates of addictive substance use compared to spatial learners who display more grey matter in the hippocampus. The CN is also involved in the perception of risk. The CN plays a central role in the reward system, and increases attention directed towards positive rewards. It is also related to the adaptation to changing reward outcomes, therefore having an importance in the learning process when it comes to positive feedback. Since the IGT offers both positive and negative feedback at the same time, and that disadvantageous decks are characterized by higher positive feedback, response learners, having higher grey matter volume in the CN, were predicted to put more importance onto rewards while putting less importance onto punishments, increasing the propensity to risk-taking within the task. Twenty-five participants were found to be spatial learners and 25 were response learners. Our results revealed that spatial learners produced significantly higher scores across all administered decks of the IGT compared to response learners. This indicated that response learners engaged in a significantly higher degree of risk

taking during the IGT, as predicted. Our results indicate that navigation strategies associated with increased grey matter in the CN are associated with increased risk taking behavior as indicated by IGT performance.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.20/HHH14

Topic: H.02. Human Cognition and Behavior

Title: Deficits in mental rotation test (mrt-a) may be correlated to higher Unified Parkinson's Disease Rating Scale (UPDRS) scores in early onset idiopathic Parkinson's disease

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Abstract: Parkinson's disease (PD) begins with unilateral symptoms (H&Y Stage I). Twenty percent of PD patients exhibit disease symptoms between the ages of 40-60 years and are classified as early-onset Parkinson's disease (EOPD). Monitoring disease progression is critical in EOPD patients as they are at an increased risk for developing motor and non-motor complications. Stage I EOPD patients without any bedside clinical evidence of dementia have shown subclinical deficits in detailed neuropsychological testing. We selected a battery of hemispheric-weighted neuropsychological tests that could be quickly administered to potentially detect these subclinical cognitive deficits. Forty-one EOPD Stage I subjects have been enrolled in this study. To account for known gender differences, the subjects were divided into the following subgroups: male right-onset EOPD (MRPD, n=11), male left-onset EOPD (MLPD, n=11), female right-onset EOPD (FRPD, n=11) and female left-onset EOPD (FLPD, n=8). Subjects were screened using the Edinburgh Handedness Inventory, Beck Depression Inventory-II (BDI-II), and the Montreal Cognitive Assessment (MoCA). Our test battery consisted of the Delis-Kaplan Verbal Fluency Test, the Mental Rotation Test Version A (MRT-A), the Delis-Kaplan Design Fluency test, the Wechsler Memory Scale Visual Reproduction I and II, the California Verbal Learning Test (CVLT-II), the Woodcock Johnson Picture Vocabulary Test and a mirror tracing task. Interim analysis showed that the MRT-A was significantly impaired compared to age-matched published controls and the right-sided EOPD subjects performing

significantly better than the left-onset EOPD subjects ($p=0.0203$) in this test. As expected, male subjects significantly outperformed female subjects ($p=0.0149$). MRPD subjects significantly scored better than MLPD subjects ($p=0.0311$). Despite lower scores, there was separation between FRPD and FLPD subjects that approached statistical significance ($p=0.0847$). Total UPDRS scores in left-onset EOPD men and women were larger than right-onset subjects, consistent with what has been reported for PD patients across all ages. Our finding suggests that there are specific visual-spatial deficits, as determined by the MRT, in stage I EOPD subjects with no clinical bedside evidence of cognitive decline or depression. This supports the notion that visuospatial deficits may account for worse PD prognosis in left-onset EOPD subjects and MRT-A could represent a biomarker for disease progression. Additional testing to clarify the relationship between MRT and PD symptomatology are ongoing and likely to provide further insights.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.21/HHH15

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01AA022493

Title: Preference for navigation based on apparatus boundaries in a virtual Morris water task is associated with increased right frontal and parietal cortical activation

Authors: *D. A. HAMILTON¹, J. COHEN-GILBERT², E. OOT³, A. SERAIKAS⁴, M. RIESELBACH⁴, L. D. NICKERSON², M. M. SILVERI², J. T. SNEIDER²

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Abstract: Apparatus boundaries and distal visual cues provide important frames of reference for navigation and spatially-tuned firing of hippocampal place cells. In the Morris water task (MWT), post-training translation of the apparatus results in a robust bias for navigation to the relative goal location within the apparatus, suggesting that distal cues support orientation and disambiguate the apparatus reference frame. In contrast, navigation to precise spatial locations defined solely by the distal cue reference frame is not observed. These patterns of outcomes have been demonstrated in humans performing a virtual MWT (VMWT), although considerable individual variation in strategies exists. In the current study, relationships were evaluated

between preference for navigation based on VMWT apparatus boundary and brain activity measured by multiband blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI). Participants included 32 (15 female, 17 male) healthy adolescents (13-14-years old), who were alcohol and drug naïve, and with no psychiatric symptoms or conditions. Prior to fMRI, participants were trained in the VMWT outside the scanner. During fMRI acquisition, participants performed interleaved blocks of hidden and visible platform trials, followed by a no-platform probe trial in which the apparatus (pool) was translated relative to the distal room cues by a distance equal to the pool radius. Time spent in two circular regions (~ 6% of the apparatus area) centered on the relative location in the apparatus and the absolute spatial location in relation to distal cues was measured. Nineteen participants displayed a strong preference for the relative location, whereas 13 participants displayed no preference or a preference for the absolute location. While Hidden trials elicited hippocampal, frontal and parietal activation, preference did not distinguish performance or brain activity. However, greater right lateralized activity in frontal and parietal regions was evident in participants with a preference for navigation to the relative location, compared to preference for the absolute location, on the Probe > Hidden contrast. No main effects of sex or interactions were observed for preference. These findings indicate that navigation and search behavior based on visual apparatus boundaries engages frontal and parietal circuits, a network implicated in spatial processing.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.22/HHH16

Topic: H.02. Human Cognition and Behavior

Title: Threat-induced anxiety selectively impairs hippocampus-mediated spatial memory, but enhances the use of striatum-based navigation, in a virtual radial arm maze

Authors: ***J. GOODMAN**, J. E. DUNSMOOR

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Abstract: The brain is composed of multiple memory systems that mediate distinct navigational strategies, including allocentric spatial navigation mediated by the hippocampus and egocentric stimulus-response navigation mediated by the dorsal striatum (i.e. caudate-putamen). Extensive evidence in rodents indicates that these distinct navigational strategies are differentially affected by emotional arousal. In particular, high levels of stress or anxiety impair hippocampal spatial memory, but enhance stimulus-response habit memory in a variety of maze learning tasks. However, the influence of emotional arousal on spatial and stimulus-response memory in

humans has not been thoroughly investigated. The present study employs a virtual eight-arm radial maze adapted from rodent learning tasks to explore the effect of anxiety on memory systems. Healthy adult participants completed either a spatial version of the radial maze (where numerous allocentric spatial cues surrounding the maze could be used for navigation) or a stimulus-response version of the radial maze (where no allocentric spatial cues are available, encouraging egocentric navigation). To modulate emotional arousal throughout the task, a sign appears during each trial and indicates the likelihood of the participant receiving an unpleasant, but painless electrical shock to the wrist. If the sign reads “SAFE,” the participant is informed they definitely will not receive a shock during the trial. If the sign reads “THREAT,” the subject is informed they can receive a shock at any time during the trial. Results indicate that in the spatial version of the radial maze, subjects make significantly more errors during the THREAT trials compared to the SAFE trials. In contrast, in the stimulus-response version of the radial maze, there is no difference between the number of errors during the SAFE and THREAT trials. In addition, participants are more likely to use a response-based serial strategy during THREAT trials relative to SAFE trials, suggesting emotional arousal enhances the use of striatal memory processes. Results are consistent with extensive prior evidence in rodents that emotional arousal impairs spatial memory, but enhances stimulus-response habit memory. Findings may be important for understanding how fear and anxiety impact the function of multiple memory systems and contribute to memory-related symptoms in human psychopathologies.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.23/HHH17

Topic: H.02. Human Cognition and Behavior

Support: RO1-MH104606
T32 Training Grant

Title: Single-neuron coding of current and goal locations in the human medial temporal lobe

Authors: *M. TSITSIKLIS¹, J. MILLER², S. QASIM², S. A. SHETH⁵, C. A. SCHEVON³, E. H. SMITH⁴, R. E. GROSS⁶, C. S. INMAN⁶, M. SPERLING⁷, A. SHARAN⁸, J. STEIN¹⁰, S. DAS¹¹, R. GORNIK⁹, J. JACOBS²

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Abstract: The hippocampus and surrounding medial temporal lobe (MTL) are known to be essential for the encoding of spatial memory. Growing evidence suggests that neurons in the MTL are modulated by viewing location and spatial goals in addition to the location that a subject is currently located in. In my research I leverage the rich literature on spatial coding in animal models to understand more broadly how the human MTL supports memory processes at the level of individual neurons. We recorded single-neuron data from patients with intractable epilepsy while they played Treasure Hunt, a video-game-like task that measures people's ability to remember links between objects and locations. In each trial patients explored a virtual beach to reach treasure chests that revealed hidden objects, with the goal of encoding the location of each encountered item. I analyzed the firing rate during navigation with respect to multiple aspects of behavior in the task, including the subject's current location, goal location, and heading direction. As expected I found that a significant proportion of MTL neurons were spatially modulated by the subject's current location (7%). Going beyond earlier work, I found that 20% of MTL neurons encoded remote locations that subjects knew they would have to remember. I also found that another 14% of cells were modulated by the subjects' heading direction. These results show that the human MTL map is flexible and not only encodes information about a subject's current location but also represents remote salient locations that are relevant for the given task.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.24/HHH18

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01-MH104606

Title: High frequency oscillations during spatial memory task

Authors: ***T. GEDANKIEN**, J. F. MILLER, J. JACOBS
Columbia Univ., New York, NY

Abstract: The ability to remember trajectories between locations is central to human experience. However, the precise neural mechanisms underlying spatial memory in humans remain elusive. In animals, previous research emphasizes two main mechanisms of memory consolidation, observed mostly during awake rest and sleep: high-frequency oscillation events, known as sharp-wave ripples (SWRs), and co-occurrent reactivation of place cells sequences, known as replay.

Here, we investigate the hypothesis that high-frequency oscillations (HFOs) in humans, like SWRs in animals, play a role in memory. After comparing and contrasting SWR and HFO literature, we further hypothesize that HFOs may be involved in both epilepsy and memory-related processes simultaneously. We analyzed intracranial recordings from epilepsy neurosurgical patients as they performed a hybrid spatial-memory virtual task. HFOs were detected by computing the envelope of the band-pass filtered signal and selecting events that were five standard deviations above the mean and displayed an isolated high-frequency spectral peak. We detected hippocampal HFOs in the 80–160 Hz band in four subjects. While some of the detected HFOs were located in previously identified seizure onset zones, these ripples often appeared at approximately the same time in electrodes from separate cortical areas—which may indicate a potential role in encoding and transfer of information. We also found that a higher number of hippocampal ripples predicted better task performance across our sample. Similar to animal SWRs, most of the identified HFOs occurred during stationary periods in the virtual task. Together, our initial results suggest that HFOs in humans are in part analogous to SWRs in animals and may concurrently convey pathological and memory-related information.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.25/HHH19

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1630296

Title: Modeling path integration in large-scale space and with novel geometries

Authors: *S. K. HAROOTONIAN^{1,2}, E. M. ZISKIN¹, E. D. ERLNBACH¹, R. C. WILSON², A. D. EKSTROM^{1,2}

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Abstract: Path integration is an important mechanism that can function with no visual input and involves employing vestibular, proprioceptive, and somatosensory inputs to track direction and distance. Theoretical models suggest that importance of error accumulation in both direction and distance to path integration in humans, although these issues have been difficult to fully test in the small-scale (roomed-sized) environments employed in most studies. The triangle completion task (TCT) is one important method for studying path integration, which involves participants integrating the distance and direction traveled through two guided legs to complete a third unguided leg, with participants returning to the origin with no visual or auditory information. Employing the triangle completion task also allows testing of the effect of different shapes of

triangles (scalene vs. equilateral vs. isosceles), allowing determination of whether participants employ geometric templates (e.g., equilateral triangle) to compensate for incomplete path integration knowledge. Here, we used an omnidirectional treadmill to test accumulation of direction and distance errors, testing a larger range of distances and triangle types than past studies. In experiment #1, we held angles constant and we manipulated distance. In experiment #2, we held the unguided leg's distance constant and we manipulated angles. In experiment #1, we found the rate of distance underestimation increased with size of the triangle. Angular error was more variable but centered at zero. In experiment #2, we found that subjects underestimated distance but overestimated angles, finding the least distance error in equilateral triangles. Angular and distance error did not correlate in either experiment. We modeled distance and angular error of the unguided leg by using the complete history and dynamics of the subject's guided legs. We hope to adapt this model to include sensory information to compare desktop VR, immersed VR, and real-world triangle completion tasks. Overall, our findings suggest that 1) the properties of path integration do not change substantially over longer distances, 2) errors in angle are more variable than those in distance 3) errors in angle and distance are uncorrelated, and, 4) there may be a bias for certain triangle types to be more readily learned than others.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.26/HHH20

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant BCS1630296 (to A. D. E.)

Title: Do frontal human cortical theta oscillations during free ambulation code spatial distance, temporal interval, or both?

Authors: ***M. LIANG**^{1,2}, M. J. STARRETT², A. D. EKSTROM²
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Abstract: Past studies have suggested the critical role of hippocampal low-frequency oscillations in spatial navigation. Additionally, cortical and hippocampal theta oscillations often synchronize, suggesting the importance of cortical oscillations to movement-related coding as well. In a recent study, we found increased scalp frontal-midline delta-theta oscillations during movement involving free ambulation when compared to standing-still in healthy humans (Liang, Starrett & Ekstrom, 2018). One intriguing question, given these findings, regards the precise

drivers of such low-frequency oscillations. While past studies have suggested spatial distance (Vass et al. 2016) and movement speed (Watrous et al. 2011) may both contribute to low-frequency oscillations, temporal components may also be a significant driver. To address this issue, participants navigated a plus maze containing four target stores at the end of each arm. Four teleporters were also dispersed in each arm involving different spatial distances and temporal intervals. In a trial, participants first entered a teleporter, and upon exiting, were teleported back to the center of a plus maze, at which time they were instructed to find a target store. In the spatial distance condition, participants judged how far they travelled inside the teleporters; in the temporal interval condition, participants judged temporal interval. On the basis of temporal interval or spatial distance (short vs. long), participants decided which target store to visit. As in the prior study, we used the omnidirectional treadmill to provide locomotion-based VR navigation experiences, simultaneously recording scalp EEG during teleportation and navigation epochs. Preliminary results showed that participants were able to discriminate between different spatial/temporal teleportation experiences at above chance levels and were able to apply the cues to find the appropriate targets. Analyses involving scalp EEG will test whether 1) frontal-midline theta oscillations persist during teleportation without the presence of visual, vestibular and proprioceptive input, regardless of spatial or temporal conditions 2) whether frontal-midline theta oscillations code space, time, or both. Our findings will help advance our understanding of the role of low-frequency oscillations in memory and navigation and deepen our understanding of the nature of “cognitive map” regarding whether a time code and a distance code co-exist in the spatial knowledge.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

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Program #/Poster #: 085.27/HHH21

Topic: H.02. Human Cognition and Behavior

Support: BMBF 01GQ1511

Title: Interactive exploration of sparse virtual environments: Brain-electric dynamics of the retrosplenial complex at salient moments of spatial thought

Authors: *L. GEHRKE¹, K. GRAMANN^{1,2,3}

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Abstract: Traditional neuroscientific imaging approaches to study human navigation neglect a central component that characterizes navigation - the multisensory experience of self-movement. We created interactive, visually sparse environments to explore event-related brain dynamics during the sequential development of spatial representations from coarse, egocentric (body-centered), to survey, allocentric (external world-centered), spatial representations in freely ambulating human participants. Our task discretizes the moments of task relevant spatial thoughts querying participants to build up a spatial representation by touching invisible walls with each touch yielding a brief visual feedback along the touched wall. Using a Mobile Brain/Body Imaging framework, we captured head and hand motion and 160 channel wireless electroencephalography (EEG) in 32 participants (aged 21-47 years, 14 men) exploring an “Invisible Maze” presented in head-mounted virtual reality (VR). Participants explored four mazes (I, L, Z, U) in three repeated trials each, with wall touches occurring in corners and dead ends defined as change and wall touches along straight segments as no-change situations. Hence, we defined a study design of 4 (mazes) X 3 (maze trials) X 2 (change or no-change situation). After each exploration, participants sketched the maze from a bird’s eye view perspective as an index of spatial learning. Two independent raters rated the usefulness of the sketches as navigational aids. Independent components analysis (AMICA) was used to separate EEG signals. ICs were clustered based on their equivalent dipole locations and time-frequency responses using repeated k-means. For each clustering solution, the cluster with the centroid located closest to the talairach coordinates of the RSC was selected and ultimately all solutions were ranked according to a set of RSC *cluster quality* criteria. Event-related spectral perturbations were calculated for the highest-ranking clustering solution. We observed an increase in efficiency in maze exploration manifested by a reduction in exploration time and wall touches in the 2nd and 3rd repetition. Meanwhile, participants either produced a useful map already after the first maze trial or were only marginally improving over time. A network of six IC clusters (frontal, motor, parietal, RSC) was identified with significant event-related perturbations in theta, alpha and beta frequency bands compared to a pre-touch baseline. Finally, testing our study design provided insights about brain dynamics of spatial cognition in mobile participants, overcoming limitations of previous brain imaging studies.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

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Program #/Poster #: 085.28/HHH22

Topic: H.02. Human Cognition and Behavior

Title: Transfer of learning: Analysis of a massive, online cognitive training dataset

Authors: *R. J. SCHAFER, N. NG, E. CORDELL
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Abstract: A central question about online “brain training” is whether and how training improvements might transfer beyond the training tasks themselves. Although some previous studies have demonstrated transfer of learning from training tasks to performance on neuropsychological assessments, there are conflicting reports about the extent of this transfer, and the “dose-response” relationship between training and cognitive outcomes is poorly described. To address these open questions, we used a large, observational dataset comprising over 300,000 individuals who underwent Lumosity online brain training and also took a battery of assessments, the NeuroCognitive Performance Test (NCPT), at two timepoints separated by several months. Individuals spanned ages (13 to 90, median of 46) and education levels. We observed a reliable, positive relationship between the amount of Lumosity training completed and the improvements on the NCPT Grand Index. Comparing individuals with very little Lumosity training (fewer than three training sessions) to those with substantial training (more than 600 gameplays), we found a moderately large effect size of training (over 0.4). The dose-response relationship reached half its maximal (asymptotic) magnitude at approximately 100 games played. By decomposing NCPT performance into its component sub-tests, we found that Lumosity training drove reliable improvements on only seven of the eight tests, consistent with published results. Through a factor analysis of NCPT subtests, we characterize the dose-response relationship between Lumosity training and multiple dimensions of cognitive performance.

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Poster

085. Human Cognition and Behavior: Human Learning: Perceptual and Spatial Learning

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 085.29/HHH23

Topic: H.02. Human Cognition and Behavior

Title: Comprehensive online cognitive training in later adulthood: An online randomized controlled trial

Authors: *N. NG, E. CORDELL, R. J. SCHAFER
Lumos Labs, Inc, San Francisco, CA

Abstract: Cognitive training has been identified by the IOM and NIH as a potentially beneficial activity for aging populations to stay cognitively engaged. In 2015, Hardy et al published a large, online randomized controlled trial comparing the effect of cognitive training, Lumosity.com, versus crosswords on neurocognitive performance in 4715 normal adults ages 18-80. In this trial, participants were randomized into two groups that were instructed to train with Lumosity or crossword puzzles for a 10-week period (15 minute sessions * 5 days/week). Participants randomly assigned to the Lumosity group improved significantly more on the primary outcome measure, an aggregate measure of neuropsychological performance (Grand Index of the NeuroCognitive Performance Test (NCPT)), than did the active control group (Cohen's d effect size = 0.255; 95% confidence interval = [0.198, 0.312]). Given the relevance of cognitive engagement for older adults, in this study we investigate the effect of Lumosity on neurocognitive performance for the subset of older adults ages 50-80 in the Hardy et al dataset -- 758 older adult participants in the Lumosity treatment condition and 570 in the crosswords control condition. An ANCOVA model measuring the effect of group confirmed that significant improvement on the NCPT for the Lumosity group compared to the crosswords group ($t(1325) = 4.28, p < 0.0001, d = 0.24$) in the older adult population. Cognitive training may also be a potential effective remediation for mild cognitive impairment and other neurological disorders associated with old age. To investigate the usefulness of Lumosity in these populations, we looked at the effects of training in a subset of participants who scored at least one standard deviation below the mean for their age group on the pre-test Grand Index score. While participants in both groups who performed at least one standard deviation below the mean for their respective age group (N Lumosity = 131, N crosswords = 78) improved on the Grand Index adjusting for pre-test score (treatment: mean = 6.79, control: mean = 1.63), these improvements were significantly greater for the treatment group compared to the control group, $t(207) = 3.17, p = .002, d = 0.44$.

Disclosures: **N. Ng:** A. Employment/Salary (full or part-time); Lumos Labs, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs, Inc. **E. Cordell:** A. Employment/Salary (full or part-time); Lumos Labs, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs, Inc. **R.J. Schafer:** A. Employment/Salary (full or part-time); Lumos Labs, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs, Inc.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.01/HHH24

Topic: H.02. Human Cognition and Behavior

Title: Controlling unwanted memories: The medial septal pacemaker suppression hypothesis

Authors: *D. APŠVALKA, M. C. ANDERSON

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Abstract: The ability to control unwanted thoughts and memories is essential to mental health and wellbeing. Prior research has found that stopping intrusive memories involves top-down control by the prefrontal cortex and subsequent inhibition of hippocampal retrieval processes. Moreover, the efficacy of this fronto-hippocampal inhibitory pathway depends on hippocampal GABA to enable memory suppression. Specifically, higher resting concentration of hippocampal GABA has predicted better mnemonic control.

These findings raise questions about the mechanisms through which hippocampal GABA enables the suppression of unwanted memories. The prefrontal cortex itself does not have direct connections to the hippocampus. Therefore, the question is, what is acting on the GABAergic interneurons in the hippocampus during memory suppression? Animal research shows that the medial-septal nucleus in the basal forebrain acts as a pacemaker for hippocampal theta oscillations necessary for memory encoding and retrieval. A pathway linking the medial-septal nucleus to the hippocampus involves GABAergic projections that terminate on hippocampal GABAergic interneurons, suppressing them and disinhibiting the hippocampus. We hypothesise that if the medial-septal nucleus itself were suppressed, it would truncate the inhibitory input to hippocampal GABAergic interneurons, raising hippocampal tonic inhibition. Subsequently, this may disrupt memory retrieval.

To investigate the medial-septal pacemaker suppression hypothesis, we hand traced the medial-septal nucleus in 330 participants in our fMRI studies of the Think/No-Think task. 103 of these participants had also provided intrusion ratings during the No-Think trials, reporting whether the unwanted memory intruded into their minds.

The results provide strong evidence for the medial-septal nucleus suppression during No-Think compared to Think trials ($d = 0.339$, $p = 2.55 \times 10^{-10}$), and especially during intrusion compared to no-intrusion trials ($d = 0.378$, $p = 2.19 \times 10^{-4}$). In ongoing work, we are investigating the interactions between the prefrontal cortex, medial-septal nucleus, and hippocampus during retrieval suppression; specificity of the medial-septal nucleus, compared to other basal forebrain structures; and resting-state functional connectivity between the medial-septal nucleus and other brain regions.

The current findings provide strong initial support for the medial-septal pacemaker suppression hypothesis. Specifically, when stopping intrusive memories, activity in the medial-septal nucleus is suppressed, potentially causing hippocampal tonic inhibition and disabling the memory recall.

Disclosures: D. Apšvalka: None. M.C. Anderson: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.02/HHH25

Topic: H.02. Human Cognition and Behavior

Support: David Winston Turner Endowment Fund

Title: The effects of physical activity and multi-day rTMS on brain network plasticity

Authors: *J. J. HENDRIKSE¹, J. P. COXON¹, N. ROGASCH¹, C. SUO¹, S. THOMPSON¹, R. DA COSTA², M. YÜCEL¹

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Abstract: Aberrant neuroplasticity is a pathophysiological trait shared by a number of psychiatric disorders. Investigating novel methods of influencing neuroplasticity may lead to new treatment approaches. Aerobic exercise (AE) and repetitive transcranial magnetic stimulation (rTMS) are individually capable of inducing neuroplasticity and improving cognitive function. AE upregulates neurotrophic mechanisms at a cellular and molecular level, while rTMS has demonstrable effects on the functional connectivity profile of particular brain networks. These two approaches may have a synergizing impact when utilised in tandem. Here we sought to determine whether regular engagement in high levels of AE can enhance the effects of multi-day rTMS. We hypothesised that physical fitness (an indirect indicator of AE engagement) interacts with the effects of high-frequency rTMS on synaptic efficacy, network connectivity, and memory performance. A sample of N=36 subjects consisting of (i) highly active individuals (> 150 minutes per week), and (ii) sedentary individuals (< 20 minutes of AE ≤ 3 times per week) completed two separate weeks of individually neuronavigated 20Hz rTMS (2s on, 28s off). A region of left parietal cortex functionally connected to a cortico-hippocampal network supporting declarative memory was targeted in one week, and a (pre-) supplementary motor area with functional connectivity to a cortico-basal ganglia network supporting procedural memory was targeted in the other. VO₂ max testing quantified cardiorespiratory fitness level, and multi-modal MRI and cognitive measures were collected pre and post to assess changes to GABA concentration, functional connectivity, and memory performance. A preliminary pooled analysis shows no significant differences to GABA concentration ($p > 0.05$, partial $\eta^2 = 0.03$) or memory

performance following multi-day rTMS to either of the targeted networks ($p > 0.05$, partial $\eta^2 = 0.01$). Relationships between observed outcomes, functional connectivity, and physical fitness will be analysed at completion of data collection ($N=40$). In contrast to past studies, our preliminary findings suggest that applying multi-day rTMS to memory networks in the healthy brain does not produce demonstrable long-lasting improvements to declarative or procedural memory. Furthermore, multi-day rTMS may not be associated with long-term changes to extrasynaptic GABA concentration, and instead may relate to other neuroplastic mechanisms, or occur at a synaptic scale where effects are indiscernible with MR spectroscopy.

Disclosures: **J.J. Hendrikse:** None. **J.P. Coxon:** None. **N. Rogasch:** None. **C. Suo:** None. **S. Thompson:** None. **R. Da Costa:** None. **M. Yücel:** None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.03/HHH26

Topic: H.02. Human Cognition and Behavior

Support: European Research Council Starting Grant (ERC -2016-STG-715714)
Biotechnology and Biological Sciences Research Council (BBSRC)

Title: Reversal of the information processing hierarchy between perception and memory

Authors: ***J. LINDE DOMINGO**¹, M. S. TREDER¹, C. KERREN¹, M. TER WAL¹, F. ROUX¹, R. CHELVARAJAH², D. ROLLINGS², V. SAWLANI², B. STARESINA¹, S. HANSLMAYR¹, M. WIMBER¹

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Abstract: It is generally assumed that the presentation of a visual stimulus (e.g. an object) initiates a processing stream that starts with perceptual features, like lines and colours, and progresses to higher levels of semantic integration that provide meaningful information (e.g. whether the object is a fruit or a tool). However, it is still unknown whether memory reactivation of these representations follows a similar hierarchical processing. In the present work, we hypothesised that retrieval follows a reversed hierarchical processing stream compared with visual perception. Specifically, we predict that reconstructing a past representation prioritizes semantic information over low-level perceptual features.

We tested this reverse reconstruction hypothesis in a series of behavioural, electroencephalography (EEG) and intracranial EEG experiments (iEEG) using an associative memory task. Participants were asked to learn a series of associations between word and images

of objects. Later, they were cued with the words and asked to remember the associated object in as much details as possible. Importantly, all objects varied along two independent dimensions: a perceptual dimension (i.e. images were presented as a photograph or line-drawing) and a semantic dimension (i.e. all images depicted animate or inanimate objects). To track the temporal processing of perceptual and semantic features in two behavioural experiments, we measured reaction times (RTs) while participants made a perceptual or semantic judgment, either when objects were visually presented, or retrieved from memory. In the two electrophysiological experiments (EEG and iEEG) we used a similar paradigm, and brain activity was recorded while participants perceived objects on the screen or reactivated them from memory. Using time-series decoding analyses, we measured in which moment brain signals allowed us to decode perceptual and semantic features during object presentation and memory reactivation.

Our behavioural and electrophysiological results support the idea of a forward hierarchical processing stream during object presentation. When seeing an object, reaction time analyses together with brain activity decoding showed that perceptual features were activated faster than semantic information. More importantly, across all experiments we consistently found a reversed processing stream during memory reconstruction, indicating that semantic information is retrieved faster than perceptual features. These robust findings suggest that memory retrieval is a multi-dimensional hierarchical process that prioritizes meaningful aspects of past events over perceptual details.

Disclosures: **J. Linde Domingo:** None. **M.S. Treder:** None. **C. Kerren:** None. **M. Ter Wal:** None. **F. Roux:** None. **R. Chelvarajah:** None. **D. Rollings:** None. **V. Sawlani:** None. **B. Staresina:** None. **S. Hanslmayr:** None. **M. Wimber:** None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.04/HHH27

Topic: H.02. Human Cognition and Behavior

Title: Cognitive and mood disorders associated with high altitude in air crew member in Nigeria

Authors: ***M. A. ADEKILEKUN**, A. Y. GUILLAUME, O. O. OLUWAFEMI
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Abstract: Cognitive and mood disorders have been reported due to altitude exposure but that in aircrew have not been widely studied. This study therefore aim to investigate cognition and mood in air- crew members. Questionnaires were administered to air-crew member immediately on arrival, to assess their attitude, mood and ability to recall some of their activities in flight. One-third of individuals rejected the data collection questionnaires on arrival due to stress they

have gone through and believing filling the form is an additional stress. One-quarter of those who collected did not respond to the tool despite the fact that it is made very brief and concise. In most of the data collected majority reflected a recall issue and mood disturbance while on flight, compared to being at their usual habitation at sea level. Therefore, more data is still being collected in some parts of the country to draw a wider conclusion.

Disclosures: M.A. Adekilekun: None. A.Y. Guillaume: None. O.O. Oluwafemi: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.05/HHH28

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant T32MH065214-11
NIH Grant R01MH094480

Title: Temporal precision of narrative free recall impacts neural patterns in the default mode network

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Abstract: When describing a specific memory, observers can vary the level of detail they provide. Some recall statements can be pinpointed to a single moment, while others summarize over longer time periods. We tested whether these two types of recall behavior are associated with distinct neural signatures, and furthermore whether the degree of summarization relates to neural pattern change between encoding and recall. In an fMRI experiment, participants watched a 50-minute movie and then described the movie events aloud in an undirected manner. Each subject's speech during the free recall session was transcribed, and each utterance was matched to its corresponding movie timepoints.

To test for effects of temporal precision, we coded the degree to which each utterance described its corresponding movie scene in a temporally specific manner. "Precise" statements pinpoint a specific and brief (<10 seconds) movie segment (e.g., "Sherlock is in the lab, and Watson and his friend walk in"). In contrast, "Summary" statements describe longer segments, often covering several consecutive events with more broad and general statements ("Watson's friend introduces Sherlock").

We investigated whether neural responses during movie viewing and subsequent recall varied by utterance type. First, we tested whether each utterance type elicited a characteristic brain state during the free recall session. We extracted voxels from the default mode network (DMN), and

selected timepoints corresponding to Summary and Precise statements. Within each subject (n=17), we calculated similarity (Pearson correlation) among multi-voxel patterns in DMN during each type of recall behavior. We observed reliable and distinct patterns when subjects made Summary versus Precise statements during free recall, such that patterns were more similar to one another within-class versus between-class. In addition, Summary statements elicited greater within-class pattern similarity than Precise statements.

Next, we measured the extent to which each movie scene was later described with Summary versus Precise statements across subjects. Across movie scenes, we observed a positive relationship between the proportion of Summary statements and the degree of “memory transformation” in posterior medial cortex (cf. Chen et al., 2016), such that movie scenes that are later summarized undergo greater systematic changes in their neural patterns between movie viewing and free recall ($r=.27$). These findings suggest that responses in this region are sensitive to the temporal precision of free recall behavior, with more summarization associated with greater pattern transformation between encoding and recall.

Disclosures: J. Chen: None. E. Musz: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.06/HHH29

Topic: H.02. Human Cognition and Behavior

Support: PSI2016-80489-P

Title: Electrophysiological signatures of event segmentation during movie viewing and recall

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Abstract: Perception and memory have been widely studied in the context of discrete pictures or words. However, in real-life, we are faced with a continuous stream of perceptual input that arrives on a wide range of timescales. Previous studies have shown that our brain can segment this continuous stream into events that not only reveal a hierarchy from coarse to fine timescales, but also integrate them differently throughout the cortex, with processing timescales increasing from tens of milliseconds in early sensory regions up to hundreds of seconds in higher-order regions. However, the neural mechanisms that support such event segmentation process during online encoding of a naturalistic and continuous experience remain unknown. To address this issue, we tested whether the formation of meaningful event models could be

expressed by specific patterns of electrophysiological activity recorded from healthy humans elicited during the online encoding of a 50 minutes movie. A Hidden Markov Model based algorithm was used to identify latent variables in the EEG and relate them to participant's later memory recall of the encoded events.

Disclosures: M. Silva: None. C. Baldassano: None. L. Fuentemilla: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.07/HHH30

Topic: H.02. Human Cognition and Behavior

Support: EU-H2020-FET 1564

Title: Hierarchical model of memory retrieval

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Abstract: In the real world, the information often exhibits multi-level hierarchical organization, such as clauses, sentences, episodes and narratives in language. Furthermore, it is well known that structured information is much easier to remember and recall than random one. To probe and quantify the brain mechanisms involved in memory structuring, we considered a memory protocol where subjects perform 'final free recall' (FFR) of several random lists of words, after each list was presented and recalled on the same day. We observed a hierarchy of grouping organizations of FFR, in particular words from same list tend to be recalled consecutively. Moreover, participants who exhibited strongest organization achieved highest level of performance. We present a simple hierarchical graph model that qualitatively capture the experimental findings. The model is based on few basic principles: (sparsity) - memory items are represented by a small group of neurons, activated when item is presented or recalled; (associativity) - previously recalled item is triggering the recall of the next item according to the size of neuronal groups simultaneously encoding both items - items similarity. Similarity values are consisted of two additive components ($Stot = S + SI$): (1) Long-terms representation similarity - random normally distributed value (S), (2) all items from the same list that were recalled in immediate free recall were assigned additional similarity (SI). Changing the grouping term (SI) we observed similarity between experimental and simulated results. More specifically, the different level of list grouping lead to similar increase in the number of words recalled; similar non-monotonic dependency of the number of sequences of words from the same list on the grouping level, similar fraction of words recalled in IFR that were not recalled in immediate free

recall. Our work suggests that human brain developed an array of strategies for structuring the information to be remembered in order to improve the subsequent recall that can be modelled within the presented framework.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.08/HHH31

Topic: H.02. Human Cognition and Behavior

Support: NIH-NINDS Grant 1RO1NS089729 to B.A.K.

Title: Competition between similar memories triggers a repulsion of their feature values

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Abstract: The hippocampus plays a critical role in disambiguating similar memories by forming distinct representations of overlapping events. Recent fMRI studies (Chanales 2017; Favila 2016; Hulbert 2014) have demonstrated that competition between similar memories drives their corresponding hippocampal patterns apart, yielding over-orthogonalized event representations. While these studies found this repulsion effect in hippocampal activity patterns, they did not record corresponding behavioral measures of feature-level memory. Here we tested the idea that repeated encoding of highly similar stimuli results in a repulsion of the feature values associated with these memories. Participants performed an associative learning task that included pairs of objects that were identical except for their color values. Each object in a pair was associated with a unique face. Thus, participants were required to discriminate the object images so that they could recall the associated face. Critically, we adjusted the similarity of the object pairs by varying the difference in hue angle between the paired objects. Pairs fell into three categories of hue similarity: high similarity (24° difference), moderate similarity (48° difference), and low similarity (72° difference). Participants learned these pairs through eight rounds of study and test. After each learning round participants completed two tests: (1) a color memory test during which participants selected the color of each object using a color wheel, and (2) an object-face associative memory test during which subjects selected the face that corresponded to each object. Immediately after all learning rounds participants completed an additional color memory test and then returned, after a 24h delay, for a final color memory test. Across learning rounds, participants' associative recall performance and object-color memory precision steadily improved. By the end of learning, participants' color memory was equally precise across the

three similarity conditions. Critically, however, the distribution of color memory estimates was strongly influenced by the level of color similarity between the object pair. Strikingly, color memory in the high similarity condition was heavily biased away from the competing object's color. This was not the case in either the moderate or low similarity conditions. This bias in color memory was also present after a 24hr delay. These results suggest that competition between highly similar events triggers a repulsion of feature values in memory, complementing recent evidence that competition triggers a repulsion of hippocampal representations.

Disclosures: A.J. Chanales: None. B.A. Kuhl: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.09/HHH32

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH103479

Title: Category selectivity and sensory reinstatement in human neocortex

Authors: *Y. Y. CHEN, D. YOSHOR, B. L. FOSTER

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Abstract: Humans have the remarkable ability to remember past events in vivid detail. According to the sensory reinstatement hypothesis, brain regions involved in stimulus encoding are reactivated to support vivid memory retrieval. Neuroimaging studies have provided evidence supporting sensory reinstatement, however the functional neuroanatomy of these effects differs between studies. In addition, neuroimaging data provides limited temporal information on reinstatement dynamics. To overcome these limitations, we utilized human intracranial electrophysiology to investigate the precise spatial and temporal properties of sensory reinstatement. We focused on category-specific reinstatement activity, namely face selectivity in the human ventral visual pathway. We asked if face selectivity was predictive of reinstatement activity during the retrieval of face stimuli. First, a visual object localizer consisting of grey-scale images from ten visual categories (faces, bodies, cars, corridors, instruments, houses, limbs, numbers, words and scrambled images) was presented to participants. Consistent with a large literature, spectral analysis identified face-selective electrodes based on changes in the high-gamma frequency range (70-150 Hz). Multiple face selective areas were identified, including the fusiform face areas (FFA: mFus/pFus) and occipital face area (OFA). Electrode location was verified through MRI/CT imaging. Next, participants performed a word-face paired associates memory task, learning to associate arbitrary words with pictures of famous faces. Participants

then had their memory tested by viewing only word cues (including old and new cues) and being asked to retrieve the associated face image. Spectral analysis revealed strong increases in high-gamma range activity during the encoding of word-face pairs in all face-selective electrodes. Interestingly, only a subset of these face-selective electrodes, localized to the mFus FFA region, displayed reinstatement activity during retrieval. Furthermore, these reinstatement effects were more temporally delayed than encoding responses and significantly larger for hits vs. correct rejection trials. These findings provide direct electrophysiological support for sensory reinstatement in human neocortex occurring within a subset of stimulus selective regions. Such a dissociation may be critical to understanding how memory-driven reactivation approximates prior perception in the absence of relevant sensory inputs.

Disclosures: **Y.Y. Chen:** None. **D. Yoshor:** None. **B.L. Foster:** None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.10/HHH33

Topic: H.02. Human Cognition and Behavior

Support: NSF EPSCoR Grant 1632738

Title: Recall dynamics of naturalistic stimuli and random word lists

Authors: ***P. C. FITZPATRICK**¹, A. C. HEUSSER², J. R. MANNING²

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Abstract: When we recall the past, our behaviors (e.g. verbally recounting an event) can never fully capture the richness of prior experience. To effectively study the dynamics of memory, one must define a “mapping function” that relates specific recall events to specific moments from our past. We can then use that mapping function to examine the sequence of timepoints or prior experiences a rememberer verbalizes. In the case of simple word list-learning experiments, humans’ intrinsic mapping functions are sufficient. We have learned through prior life experience that certain sounds (vocalized words) and letters on a computer screen (written words) map onto each other and bear the same meaning. We then leverage these learned mappings to match up specific verbalized recalls with specific studied words. However, in naturalistic learning tasks (e.g. recalling stories, movies, or real-life experiences), those mappings between stimuli and vocalizations are necessarily underspecified. In other words, a verbal description cannot capture the full visual detail of a movie frame, complex sound sequences, intricate emotions, the contextual framing of an experience, etc. Therefore, studying recall dynamics in naturalistic learning tasks requires defining mapping functions between verbal

recalls and rich naturalistic experiences that are robust to specific wording choices. Rather, the mapping functions must capture the underlying content of the original experiences. Here we employ topic modeling (Blei et al., 2003) to capture the dynamic semantic content of naturalistic stimuli (a movie) as well as verbal recalls of the content of the movie (data from Chen et al., 2016). The models yield a series of feature vectors that reflects the semantic content of each moment of the stimulus and recall sequence. We then define a mapping function that describes which moment(s) of the movie each moment of recall reflects. This allows us to study detailed recall dynamics of complex naturalistic stimuli, in much the same way that prior work has examined the detailed recall dynamics of far simpler stimuli, such as random word lists (e.g. see Kahana, 2011). We also provide an open source toolbox for applying our approach to experimental data (Heusser et al., 2017).

Disclosures: P.C. Fitzpatrick: None. A.C. Heusser: None. J.R. Manning: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.11/HHH34

Topic: H.02. Human Cognition and Behavior

Support: ERC Grant 647954

Title: Probing hippocampo-neocortical communication with direct electrical stimulation in humans

Authors: *M. VAN DER PLAS¹, F. ROUX¹, D. T. ROLLINGS², R. CHELVARAJAH², V. SAWLANI², S. HANSLMAYR¹

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Abstract: The act of remembering any past event, or the creation of a new episodic memory, relies on effective communication between the hippocampus and the neocortex. However, we have a limited understanding of the electrophysiological signature of these communication pathways and their mechanisms. The recently proposed computational model, the Sync/deSync Model by Parish et al. (2018), addresses this question by suggesting that the hippocampus responds to stimulation (sensory or artificial) with synchronization (i.e. theta power increases) whereas the neocortex desynchronizes (i.e. alpha/beta power decreases). Deriving our working hypotheses from this model, we investigated the electrophysiological responses in the hippocampus and neocortex with brief electrical bipolar single pulses which were delivered in the hippocampus and various neocortical areas in epileptic patients (N=4) under clinical

observation. This approach allows to causally test the hippocampo-neocortical communication pathways and their functional signatures. All patients were implanted with hybrid macro-micro electrodes, which allows for recording of single and multi unit activity as well as LFP activity. A preliminary analysis has shown that the hippocampus and the cortex exhibit increased neural activity following a pulse. Furthermore, there seems to be a reasonable conduction delay between hippocampal and cortical activity when compared to conduction delays evident from correlational studies investigating the storage and retrieval of memory traces. Another branch of the analysis focusses on the oscillatory activity in both the hippocampus and the cortex, following a pulse in either of them. The last branch of analysis concerns the single-unit and multi-unit activity following pulses in the hippocampus or the cortex. The results of this analysis will test the specific predictions derived from the Sync/deSync Model. This will broaden our understanding of how the hippocampus and cortex communicate what the electrophysiological signatures of this communication are.

Parish, G., Hanslmayr, S., & Bowman, H. (2018). The Sync/deSync Model: How a Synchronized Hippocampus and a Desynchronized Neocortex Code Memories. *Journal of Neuroscience*, 38(14), 3428-3440.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.12/HHH35

Topic: H.02. Human Cognition and Behavior

Support: NIH

Title: Predicting sleep-dependent memory consolidation from EEG activity during initial encoding

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Abstract: A large body of evidence has shown that sleep plays a critical role in the consolidation of memories. It is less clear how the brain selects and prioritizes which memories undergo sleep-dependent consolidation. Our previous behavioral studies have suggested the strength of a memory at the moment of encoding is an important prioritization mechanism. This study extends our previous work by using EEG to identify neural signatures of memory strength at encoding,

and using them to predict consolidation during sleep. Participants (n = 18) learnt pairs of words at a computer, with the number of presentations of each item manipulated in order to induce different levels of encoding strength. Participants then performed a free recall task. Following that half of the participants (n = 8) had a 2-hour nap opportunity, whilst the rest (n = 10) remained awake. At the end of the day, participants took part in delayed recall test. Brain activity was recorded throughout with EEG. Preliminary findings suggest less forgetting between recall sessions in the nap group compared to the wake group. In addition, the nap group prioritized the consolidation of weakly encoded information over more strongly encoded items. These behavioral results replicate our previous studies, and show that sleep prioritizes the consolidation of weakly encoded information in a nap paradigm. This behavioral effect allows us to now look at how neural activity at encoding can be used first to categorize memory encoding strength, whether this EEG signature predicts memory consolidation, and if this relationship is mediated by sleep spindle activity. Data collection from additional participants is ongoing.

Disclosures: **D. Denis:** None. **R. Stickgold:** None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.13/HHH36

Topic: H.02. Human Cognition and Behavior

Support: NIH-NINDS 1R01NS089729 to B.A.K.

Title: The cortical locus of stimulus representations is influenced by the state of the memory system

Authors: ***N. M. LONG**¹, S. E. FAVILA³, B. A. KUHL²

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Abstract: When you encounter a colleague whom you've previously met, you may find yourself trying to retrieve details about this colleague only to realize that you have failed to register what they are presently saying to you. This example reflects an important tradeoff: retrieving past information about a stimulus can come at the expense of encoding new information about that stimulus. Interestingly, this tradeoff also potentially relates to the cortical regions that are involved in representing stimulus information. Namely, during memory encoding tasks, stimulus representations are relatively stronger in visual cortical regions, whereas during retrieval tasks representations are relatively stronger in frontoparietal regions (Xiao et al., 2017). Here, we tested a novel prediction that in situations where a given stimulus can either elicit encoding or

retrieval (as in the example above), the state of the memory system (encoding vs. retrieval) will be directly related to the cortical locus of stimulus representations (i.e., representation in visual vs. frontoparietal regions). We tested this idea in a human fMRI study. The experiment consisted of two phases: in phase 1, participants viewed a set of object stimuli. In phase 2, participants viewed a set of new object stimuli, but each new object was categorically related to an object from phase 1 (e.g., if participants saw a bench during phase 1, they would see a new bench during phase 2). Critically, during phase 2, participants were cued, just before each object appeared, to either 'retrieve' (think back to) the related item from phase 1 or to 'encode' the newly presented item. Importantly, even when the instruction was to retrieve, participants still had to process the new item in order to know which item from to retrieve from phase 1. Thus, encode and retrieve trials were perceptually matched. To measure stimulus representations, we repeatedly presented the same objects (with the same encode/retrieve cue) across multiple runs. Using representational similarity analyses, we measured the strength of object-specific representations separately during encode and retrieve trials. Additionally, using pattern classification, we tested whether encoding and retrieval were discriminable neural states. We found that visual cortex reliably represented objects during both retrieve and encode trials, whereas frontoparietal regions preferentially represented objects during retrieve trials. Moreover, memory state (encoding vs. retrieval) was reliably decoded from distributed cortical patterns and decoded state information was related to the locus of stimulus representations.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.14/HHH37

Topic: H.02. Human Cognition and Behavior

Title: Separation of items from their context observed via fMRI pattern analysis of item-method directed forgetting

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Abstract: Context-change theory of list-method directed forgetting (DF) proposes that changes in context associated with to-be-forgotten items is a mechanism for successful forgetting (e.g., Sahakyan & Kelley, 2002). Context processing has been investigated in list-method DF paradigm, including a recent study that used multi-voxel pattern analysis (MVPA) of fMRI data

to show that people can intentionally forget previously experienced events by changing their mental representations of contextual information associated with those events (Manning et al., 2016). To date, there has been no comparable investigation in the item-method DF paradigm. The purpose of the current study was to directly examine the role of context information in an item-method DF study using MVPA of functional imaging data. Specifically, we hypothesized that, as in list-method DF, the modification of context information plays a role in the intentional forgetting of individual items. In the first phase, participants viewed trials consisting of a negative or neutral word. Critically, we “tagged” the mental context during this encoding phase by presenting task-irrelevant scene images between trials (Gershman et al., 2013). This led participants to form incidental associations between items (words) and the encoding context (scenes). The studied words (but not the scenes) were then presented again in an item-method DF phase, where each word was followed by an instruction to either forget or remember the word. fMRI pattern classifiers were trained (from a separate localizer task) on activity in the ventral visual stream to identify activation patterns associated with words and scenes. These classifiers were then applied to data from the DF phase to provide a measure of item and context processing. Preliminary results indicate that after a forget instruction, the amount of item information (classifier evidence for “word”) dropped below the pre-cue period, and was markedly lower than after remember instructions. This may reflect deactivation of the to-be-forgotten item. Context information associated with the studied words was reactivated before the DF instruction (i.e., an increase in classifier evidence for “scene”). Interestingly, after a forget instruction the amount of context information increased relative to the pre-cue period and it was stronger than after a remember instruction. Together, this selective decrease in item information and increase in context information may reflect the active unbinding of an item from its context. Taken together, this study provides the first demonstration of the differential processing of item and context information in item-method directed forgetting.

Disclosures: Y. Chiu: None. T.H. Wang: None. D.M. Beck: None. J.A. Lewis-Peacock: None. L. Sahakyan: None.

Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.15/HHH38

Topic: H.02. Human Cognition and Behavior

Title: Event-related brain responses to lexical encoding exposures predicts subsequent false endorsement of orthographically related lures

Authors: *N. R. GRIFFIN, B. ASFAW, T. BRANS, D. MARQUEZ, S. WEYSER, C. YEE, D. M. SCHNYER

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Abstract: Memory research shows event-related brain potentials (ERP) recorded in humans during encoding predict subsequent remembering, which can be dissociated by valence. These differences predicting subsequent memory (Dm), present as greater early frontal scalp potentials for A) trials leading to remembered (hits) versus forgotten (miss) responses, and B) for emotional versus non-emotional items. The present research leveraged the Dm effect to better understand processes contributing to false remembering by valence. False memory studies show ERPs for hits and false remembering are highly similar during time of retrieval; activation differences only emerge late after stimulus onset. Thus, Dm effects may be similar for encoding trials predicting subsequent hits and for encoding trials associated with subsequently falsely remembered items. We used an orthographic adaptation of the DRM false memory paradigm to control connotative and valence-related priming and more directly test false memory responses. Participants encoded lists of words 1-2 letters different from each other, each associated with an unstudied word, or critical lure. They completed a recognition memory test including randomly selected words from encoding (old), associated critical lures (lures) and novel words. We did not find an interaction of emotion for Dm effects, so subsequent analyses were collapsed across valence. We found: 1) Old item Dm; a more positive potential around 400ms over left central and parietal scalp regions during encoding for subsequent hits relative to misses. 2) Lure Dm; a more negative potential around 300ms over bilateral frontal and central scalp regions for subsequent lure false alarms (FAs) relative to correct rejections (CR). 3) Significantly more positive amplitudes late after stimulus onset over bilateral frontal and central scalp regions for subsequent lure FAs versus CR. Interestingly, the old item Dm was found over central and posterior scalp regions, potentially corresponding to relatively recollection-based retrieval. We found no Dm differences between encoding trials predicting subsequent hits and trials associated with falsely remembered items. Thus, encoding processes that contribute to memory accuracy may also be associated with later erroneous memory retrieval.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.16/HHH39

Topic: H.02. Human Cognition and Behavior

Support: DARPA-RAM Cooperative Agreement N66001-14-2-4032

Title: High and low frequency stimulation have inverse effects on neuronal activity

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Abstract: Brain stimulation shows enormous clinical potential as a treatment for a variety of neurological conditions; however, we do not yet have a detailed understanding of how stimulation alters underlying brain activity. In particular, there is only a fairly small literature on the how direct cortical brain stimulation has excitatory and inhibitory effects of stimulation on local and connected regions. We investigated the effects of direct electrical stimulation on the human brain to understand how changes in stimulation location, amplitude, frequency, and duration induce changes in activity across the brain. We collected human electrocorticographic recordings from 111 neurosurgical patients while stimulation was systematically delivered for different combinations of stimulation location, amplitude, frequency, and duration. We calculated spectral power before and after the delivery of stimulation and mapped changes across the brain in the distribution of high frequency activity (30-100Hz) neural activity, which is a marker of mean neuronal activity. Electrodes local to lateral-temporal-lobe stimulation sites showed both increases and decreases in high frequency activity power. By examining this effect based on the frequency of stimulation, we found that low frequency stimulation caused neural inhibition of high frequency activity and high frequency stimulation caused excitation. We also found sites where stimulation demonstrated a new phenomenon, ‘resetting’, where stimulation at multiple frequencies caused the power of high frequency activity to go to a particular fixed level. This phenomenon may relate to stimulation disrupting or resetting memory states. These results suggest that specific stimulation frequencies may be chosen based on the desired changes to high frequency activity when modulating behavior and cognition.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.17/HHH40

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant AG19731

Title: Presentation order at encoding is reflected in exemplar-specific reinstatement during word memory retrieval

Authors: *E. A. WING¹, B. R. GEIB², Z. A. MONGE³, W.-C. WANG³, R. E. CABEZA²
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Abstract: Items presented at the beginning or end of lists are often remembered better than those presented in the middle. This well-known serial position effect exerts a powerful influence on memory across a range of contexts and has been studied extensively over the decades. Typically, the mnemonic consequences of serial position are examined using unique, differentiable stimuli, where recall or recognition can be mapped back to the corresponding temporal or sequential position of an item at encoding. The effects of serial position are less clear in cases where memory for a general concept might be attributable to any number of specific instances matching the concept. For example, remembering that a nearby furniture store sells lamps may be based on seeing one lamp in particular, or on an overall gist created by seeing many different lamps. In the present fMRI study, we tested whether general concept memory reflects the disproportionate retrieval of specific concept instances by comparing patterns of brain activity during encoding and retrieval. Participants first viewed six different picture exemplars of various object concepts (e.g. six different bicycle pictures) at encoding. The following day, memory was tested during a word recognition (the word “bicycle”) phase that also contained new distracter words. Following past neuroimaging work on the reactivation of encoding-related patterns at retrieval, we compared cortical similarity at word recognition to the evoked patterns of each encoding exemplar. In several regions of ventral visual stream, patterns for recognized words more closely matched the initially shown exemplar than subsequently presented exemplars, consistent with a primacy effect. To further examine serial position, we used convolutional neural networks to build models expressing the conceptual similarity between different object pictures at encoding. In overlapping ventral stream regions, this cross-stimulus analysis revealed that patterns evoked by word retrieval most closely matched stimulus models created from initially presented object exemplars, rather than models created from subsequently-presented exemplars. Together these results suggest that retrieval of a general concept may be differentially based on individual instances from encoding in a way that reflects the influence of serial position.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.18/HHH41

Topic: H.02. Human Cognition and Behavior

Support: Valentine Fund
Dean's Student Research Fund

Title: Changing memory via reconsolidation: A web-based intervention for reducing intrusive memories

Authors: *S. V. ONYPER, S. C. HENEGAN, R. J. MUSKIN, T. LAROBARDIERE
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Abstract: Traumatic events often lead to intrusive memories that may hinder people from performing their daily activities. Due to high prevalence of trauma, it is important to find interventions that can reduce intrusive memories for someone with a recent traumatic experience. In the current study, healthy participants watched a ten-minute film consisting of clips of cinematic injury, death, and mutilation to induce intrusive memories. Twenty four hours later, the memories of the clips were reactivated, following which the participants were split into two groups. The treatment group played Tetris, a game where one rotates and arranges blocks in rapid succession, for 15 minutes, and the control group rated pieces of music for various characteristics. Prior work has shown that Tetris, when played shortly after an emotional memory is reactivated, can effectively reduce that memory via reconsolidation, a process of memory updating that occurs whenever a memory is retrieved. Both groups recorded the number of intrusive memories they experienced for one week after the intervention. Participants in the treatment group reported significantly fewer intrusive memories than the control group, albeit the effect was modest and variable. The sources of variability are an important avenue for further research. Nonetheless, the study's manipulation may serve as an effective, easily accessible, and affordable means to reduce traumatic memories.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

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Program #/Poster #: 086.19/HHH42

Topic: H.02. Human Cognition and Behavior

Title: Memory strengthened by repeated labilization-reconsolidation process: A resting state EEG study

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Abstract: Consolidated memories can persist from a single day to years, and persistence is improved by retraining or retrieval-mediated plasticity. Memory enhancement has a fundamental role in the maintenance of memory relevance. One retrieval-based way to strengthen memory is the reconsolidation process. This mechanism occurs when a consolidated memory is reactivated by the presentation of a reminder which represents an incongruence between past and current events, generating an error in the prediction. In humans, it was shown that the presentation of more than one of these reminders improves the performance in the testing session by enhancing memory precision. Here, we tried to make a step forward in the identification of brain correlates imprinted during the reconsolidation process of a syllable-paired association task after the reactivation. We suggest that the brain at rest is a potential gateway to understand the brain plasticity that is occurring during the memory enhancement. The aim of this study was to analyze the power spectra and EEG connectivity of the resting state immediately after the three different reactivation conditions: the presentation of one cue that included the prediction error and triggered the labilization-restabilization process (Rx), the presentation of two consecutive Rx (Rx2) and the presentation of a reminder that not labilized the original trace. The reminders that triggered the reconsolidation process were associated with an increase in whole brain theta and low beta band. Moreover, the condition that involved the double reactivation performed better in the testing session 48 hours after training and presented the highest theta power (between 4 and 8 Hz) in frontal regions as in encoding and retrieval of episodic memory tasks. In addition, the Rx2 condition present an increase of all oscillation bands in the whole brain which supports previous findings where the retrieval of memories that passed through the reconsolidation process are associated with a larger and more connected brain network, involving a better exchange information.

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Poster

086. Human Cognition and Behavior: Human Long-Term Memory: Encoding, Retrieval, Reconsolidation

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 086.20/HHH43

Topic: B.08. Intrinsic Membrane Properties

Support: Initiative d'Excellence de l'universite de Bordeaux
ANR

Title: Neural allocation mechanisms of remote memories

Authors: *I. DEL PINO¹, S. HADZIBEGOVIC², L. ZHU³, M. GINGER³, O. NICOLE⁴, B. BONTEMPI⁵, A. FRICK¹

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Abstract: During the course of system's level consolidation, memories are stored and stabilized gradually within the prefrontal cortex (PFC). Previous findings suggest that an early tagging of immature memory engrams in the PFC is required for permanent storage of long-lasting memories. Although many studies support the role of synaptic plasticity as critical factor during learning for the integration of neurons into active memory engrams, the biological mechanisms responsible for the gradual consolidation of memories in the PFC remain poorly understood. It is hypothesized that intrinsic plasticity mechanisms - changes in neuronal excitability - play a profound role during memory formation. We have combined mouse genetics with behavioral as well as electrophysiological approaches, to address whether intrinsic plasticity is part of the tagging process required for the formation of enduring memories in the PFC.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.01/HHH44

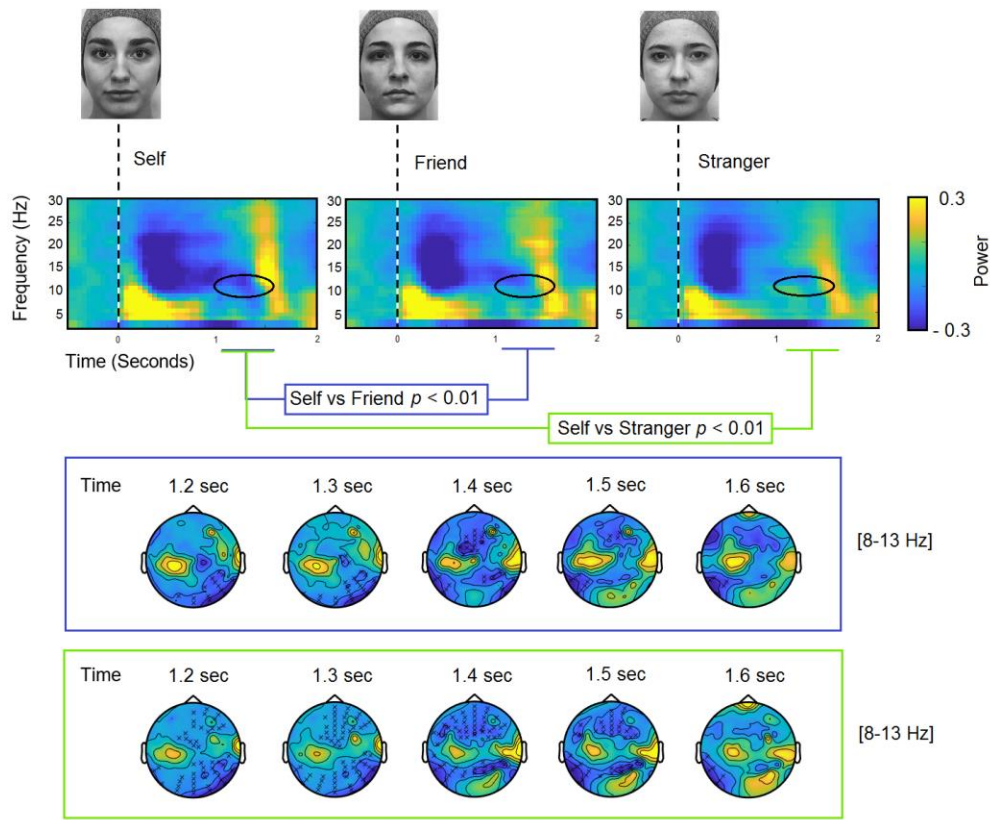
Topic: H.02. Human Cognition and Behavior

Support: Spanish Ministry of Economy and Competitiveness (MINECO) (UAMA13-4E-2192)

Title: Alpha band suppression and the maintenance of attention for the self-face

Authors: *E. RODRÍGUEZ ALZUETA¹, M. MELCON¹, O. JENSEN², A. CAPILLA¹
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Abstract: It is well known that processing of information related to ourselves prevails over information related to other people. This self-advantage is called the “self-bias effect”. Although evidence shows clear inter-relations between attention and self-related information, a central question remains: is self-bias dependent on attention or can self-relatedness be computed pre-attentively? The present study aimed to clarify this question using the own participant’s face, as a unique self-related stimuli, in a face recognition task. Twenty-five healthy participants were asked to identify their own face, a familiar face and a stranger face while their EEG activity was recorded using a Biosemi 128 channels system. Our behavioural results replicated the self-bias effect in self-face recognition, that is, participants were significantly faster recognizing their own face than other faces. In addition, time-frequency analysis revealed a sustained alpha band suppression (8-13 Hz) after stimuli onset in occipital and frontocentral sites. Interestingly, alpha band desynchronization lasted longer for the self-face (i.e. up to 1.6 seconds) compared to other faces (see Figure 1), which might be reflecting an enhanced and sustained engagement of attentional resources to the own face. Furthermore, sustained alpha band activity differed between processing the own face and a familiar face, ruling out the possibility that the self-bias might be simply accounted for by a familiarity effect. These findings provide support to the notion that the self-bias effect is due to an increased attentional deployment to self-related stimuli once perceived, rather than to an early attentional capture.



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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.02/HHH45

Topic: H.02. Human Cognition and Behavior

Title: Does vulnerability of cognitive impairments under ethanol and sleep deprivation share the same molecular basis in humans?

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Abstract: Background: Modern work environments promote irregular and restricted sleep times at the cost of increased fatigue and human error. Trait-like differences in performance after sleep loss put some individuals more at risk than others. These performance variations exist also for the acute effect of alcohol. We therefore examined whether performance variations induced by either alcohol or sleep deprivation are personality traits based on individual response mechanisms. Since sleep-deprivation induces changes of adenosine receptor levels we hypothesized that ethanol might pose similar effects on cerebral A1 adenosine receptor (A1AR) availability and used positron emission tomography (PET) for individual quantification.

Methods: Sustained attention performance (Psychomotor Vigilance Task, PVT) was tested in 49 healthy volunteers (26 ± 5 years, 15 females) under 1) baseline conditions, 2) after alcohol intake and either after 3A) total sleep deprivation (TSD, 35 h awake, $n=35/49$) or after 3B) partial sleep deprivation (PSD, 5 nights with 5 h sleep, $n=14/49$). Ethanol-induced changes in cerebral A1AR availability were measured in 10 healthy male volunteers (31 ± 9 years) with [¹⁸F]CPFPX PET. The degree of performance degradation was calculated as deviation from baseline performance.

Results: Highly significant correlations between the performance impairments by ethanol and sleep deprivation were found for various PVT parameters such as mean reaction time (TSD $r=0.66$, PSD $r=0.82$, Spearman). A1AR availability showed an acute increase in several brain regions after ethanol infusion. **Conclusion:** There are individual trait characteristics for being either vulnerable or resilient to both alcohol and sleep deprivation. Both of them induce gradual increases in cerebral A1AR availability pointing to a potential common molecular response mechanism.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.03/HHH46

Topic: H.02. Human Cognition and Behavior

Title: Right intraparietal sulcus (rIPS) modulates the effect of irrelevant salience signals located outside the spatial attentional focus

Authors: S. BERTLEFF¹, G. R. FINK^{1,2}, *R. WEIDNER¹

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Abstract: Spatial attention modulates the impact of involuntary attentional shifts to highly salient but irrelevant stimuli outside the top-down attentional focus (Theeuwes, 2010). Successfully overcoming bottom-up driven selection of unattended distractor stimuli does not depend on a reduced coding of their salience in early visual regions, but seems to operate on later processing stages (Bertleff et al., 2016). However, the neural mechanisms underlying the modulatory effect of top-down focused spatial attention on salience-based attentional orienting toward unattended irrelevant distractors remain to be elucidated. The effect of top-down spatial information on attentional orienting processes has often been investigated using Posner's paradigm (Posner, 1980) in which a cue indicates the upcoming target location with certain validity to allow a prior engagement of attention at that location. The extent to which attention is actually engaged at a cued location modulates the effort to modify the current spatial attentional set e.g., when the cue is invalid and reorienting toward an unattended target location is required (Vossel et al., 2006). In the present study, two separate fMRI experiments were conducted to test for functional commonalities between the processes involved in reorienting attention in the context of high spatial attentional engagement and in compensating salience-based distraction at locations outside the top-down spatial focus. One experiment identified the brain regions involved in overcoming attentional capture by using the additional singleton paradigm (Theeuwes, 1991) in combination with spatial cueing and demonstrated that efficient compensation of attentional capture at unattended salient distractor locations activated the rIPS. In a second experiment, a variant of Posner's paradigm was used to test the involvement of this particular brain area in attentional reorienting in the context of high and low initial attentional engagement. The region in the rIPS that was involved in neutralizing attentional capture showed increased BOLD signals when reorienting was required under conditions of high attentional engagement thus indicating its involvement in adjusting a strong spatial attentional set. In sum, our data show that the processes involved in modifying a top-down attentional set and those assisting to overcome salience-based capture draw upon common brain regions. This suggests that focusing spatial attention on a top-down defined location implements a strong attentional set that counteracts bottom-up orienting triggered by competing salience signals of irrelevant distractors thereby neutralizing capture effects.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

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Program #/Poster #: 087.04/HHH47

Topic: H.02. Human Cognition and Behavior

Support: MEXT KAKENHI Grant Number 16K00199 to TK

Title: Timing and binding: Temporal attention modulates illusory-figure perception via subjective arousals

Authors: *T. KASAI¹, S. MAKINAE², K. KITAJO³, A. FUJI¹

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Abstract: Visual grouping or completion is often referred to as an automatic and basic function to build up objects or processing units for higher cognitive processes. However, it requires large-scale cortical integrations and could be a task that consumes processing resources. This study examined effects of temporal attention or expectation with rhythmic stimulus presentation on event-related potentials (ERPs) and gamma-band responses associated with Kanizsa-type illusory figure perception. We also focused on arousals as a critical factor for attention. Twenty-six healthy adults participated and were divided into three groups (high, middle, low) based on subjective-arousal scores of an affect grid that they filled before experimental runs. Four packmen, directed inward to form an illusory square (Kanizsa figure) or outward (control), were presented at the center of the display with duration of 50 ms. Stimulus-onset asynchronies were fixed 1500 ms (regular blocks) or jittered in 900-2100 ms (irregular blocks), the order of which was counterbalanced across participants. The task was to judge the direction of arrow (left, right), infrequently presented (1/3), but simultaneously with packmen at the center of the display during EEG recordings. ERP calculations and time-frequency analyses were conducted after ICA-based artifact removal using electro-oculograms. In behavioral data, reaction times (RTs) decreased in regular compared to irregular blocks and for Kanizsa compared to control stimuli, which respectively show effects of temporal attention and illusory-figure formation. RTs were also faster for the high-arousal group than the low group and significantly decreased as arousal scores increased ($r=-0.48$). In contrast, P1 and N1 peak latencies (around 110 and 170 ms poststimulus) of ERPs over occipito-temporal sites were shortest for the middle group. Importantly, ERP figure effects were found as shorter P1 and N1 latencies for Kanizsa figure, and the P1 effect increased for regular compared to irregular blocks only in the middle-arousal group. A similar pattern of results was observed for the size of occipital gamma-range (30-40 Hz) phase locking factor at 70-100 ms. These data suggest that moderate arousals facilitated deployment of attention to the timing of stimulus occurrence in regular blocks, which facilitated illusory-figure formation. Thus, early cortical integration processes could be more vulnerable than generally believed and arousals and temporal distributions of attention should be considered for understanding clinical as well as healthy populations who show atypical global perception.

Disclosures: S. Makinae: None. K. Kitajo: None. A. Fuji: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.05/HHH48

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Council (United Kingdom), program SUAG/002/RG91365

Title: Representation of task episodes in human cortical networks

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Abstract: Task episodes consist of temporally organized sequences of steps that occur within a given context. Whenever a step is completed, its specific content loses relevance, but higher level task representations of the full episode must remain in behavioral control. The current study used fMRI to examine which regions represent full episodes, items within the episode, and current position in the episode. Prior to the experiment, participants learned 6 tasks that each consisted of 4 steps (e.g., “make a stew” consisted of “take food from fridge”, “wash vegetables”, “chop vegetables”, and “cook on stove”). Inside the scanner, participants carried out a continuous “execution” task, in which after being cued which task to perform, participants were asked to sequentially identify the target item of each step in the correct order. Univariate analysis showed progressively higher activation towards the end of the task episode in the default mode network, along with regions irrelevant to the task (e.g. auditory cortex). In contrast, early visual cortex showed progressively decreasing activity. Next, FIR parameter estimates showed that ‘task-positive’ regions, including the visual cortex, frontoparietal network, and dorsal attention network, showed clear phasic response to the execution of each task step, suggesting that they are sensitive to the fine structure of the contents within a task. In contrast, core default mode regions showed gradual change throughout the entire task. Lastly, a representational similarity analysis was performed to identify coding of full episodes, items, and position in predefined networks. Analysis of episode and item coding revealed a significant dissociation between ‘task-positive’ regions and the default mode network. Compared to ‘task-positive’ regions, which showed higher coding of individual items compared to the entire episode, the default mode network showed no preference of item and episode. All networks exhibited significant coding of temporal position. This study suggests that broad brain networks are involved in executing task sequences, and that different networks may differentially represent individual task components and entire task episodes.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: 087.06/HHH49

Topic: H.02. Human Cognition and Behavior

Support: This research was supported by Bursaries award 211/16 from the BIAL Foundation.

Title: Going offline: Spontaneous alternation between "online" and "offline" waking states

Authors: T. SUMMER¹, *E. J. WAMSLEY²

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Abstract: Rest is often considered a waste of time. Yet new evidence suggests that this is far from the case -- "offline" periods may serve a critical role in memory consolidation. Indeed, 15min of eyes-closed rest following learning significantly boosts memory for up to one week. Could even briefer periods of rest during the day also support consolidation? Evidence from animal models and human studies of mindwandering suggests that we spontaneously switch between two opposing attentional states - one in which we attend to the external world ("online") and one in which we disengage from the sensory world to focus our attention internally ("offline"). We aimed to create a data-driven model of alternation between "online" and "offline" attentional states in human subjects. N=37 participants encoded a verbal learning task prior to a 30min retention interval in which they completed a sustained attention to response task (SART) with high density EEG and pupillometry recording. Of 324 5sec trials, 24 were "probe trials" in which participants indicated current focus of their subjective experience. An EM cluster analysis was applied to all probe trials to define attentional states in a data-driven manner using EEG spectral power, along with reaction time (RT) to SART stimuli, pupil diameter, and subjective experience data. Subsequent to clustering, developed a naive Bayes algorithm that categorized trials as either "online" or "offline" with over 95% accuracy, without utilizing subjective experience probes. This classifier was then applied to label all 324 trials as either "online" or "offline". Optimal cluster separation was obtained with 2 states. In line with our hypotheses, participants spent an average of 57% of the retention interval in an "online" state characterized by fast RT, attention to the SART, and low alpha, and 43% of the interval in an "offline" state characterized by slow RT, daydreaming, and high alpha. Pupil size did not differ between "online" and "offline" states, but did vary according to participants' subjective assessment of their attentional focus. There was a trend for time spent offline to predict subsequent memory for one of two tasks examined ($r=0.31$, $p=0.1$). These observations are consistent with the hypothesis that seconds-timescale alternation between online and offline states is a fundamental feature of wakefulness. The machine-learning methods employed here may prove useful for future research describing the microstructure and function of offline

waking states. The trend association between offline time and memory retention warrants further research exploring a potential memory function of brief periods of spontaneous offline time.

Disclosures: T. Summer: None. E.J. Wamsley: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Topic: H.02. Human Cognition and Behavior

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Title: Neural mechanisms of sustained attention are rhythmic

Authors: *R. F. HELFRICH¹, I. C. FIEBELKORN³, S. M. SZCZEPANSKI¹, J. LIN⁴, J. PARVIZI⁵, R. T. KNIGHT², S. KASTNER³

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Abstract: Classic models of attention suggest that sustained neural firing constitutes a neural correlate of sustained attention. However, recent evidence indicates that behavioral performance during sustained attention fluctuates over time, exhibiting temporal dynamics that closely resemble the spectral features of ongoing, oscillatory brain activity. Given that neural activity is inherently time varying, it has been proposed that periodic fluctuations in neuronal excitability might shape attentional allocation, perceptual sensitivity and overt behavior on a rapid time scale. However, empirical evidence in humans to support this notion is sparse. Here, we address this issue by examining data from large-scale subdural recordings in 15 epilepsy patients, who underwent pre-surgical evaluation, with widespread coverage of frontal and parietal cortex. We utilized two different attention tasks that track perceptual ability at high temporal resolution (Fiebelkorn et al., 2013; Szczepanski et al., 2014). Our results reveal that perceptual outcome varies from moment to moment as a function of the theta phase around 4 Hz, even in states of sustained spatial attention. We further demonstrate that theta phase predicts instantaneous cortical excitability as indexed by high-frequency band activity (HFB; 70-150 Hz) and

coordinates information flow in the frontoparietal attention network. These effects were robust at the single-subject level and were observed during both behavioral tasks, suggesting that rhythmic perceptual sampling is an inherent property of the frontoparietal attention network. Collectively, these findings demonstrate that human behavior varies as a function of endogenous population activity and support the notion that the functional architecture of top-down attention is intrinsically rhythmic.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.08/HHH51

Topic: H.02. Human Cognition and Behavior

Title: Interactions between the superior colliculus and the lateral tegmental nucleus in the mouse

Authors: ***N. B. KOTHARI**, W.-K. YOU, S. P. MYSORE
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Abstract: Selecting the most important stimulus for spatial attention is an important aspect of adaptive behavior in animals. Recently it has been shown that the optic tectum (OT) and its GABAergic satellite nucleus, the isthmi pars magnocellularis (Imc), play a crucial role in competitive stimulus selection across space. Similarly, it is well established that the superior colliculus (SC - the mammalian homolog of the OT) plays an important role in target selection for spatial attention. Little is known, however, about the periparabigeminal lateral tegmental nucleus (pLTN - the mammalian homolog of GABAergic Imc). In this study we use retrograde viruses with different reporters to trace the anatomical connectivity between the SC and the pLTN. Further, using genetically-based techniques for manipulating neural activity, we establish the functional connectivity between these two brain regions. Understanding the anatomical and functional interactions between these two important midbrain regions is imperative to further understand how the brain selects the most important stimulus in the environment for behavior.

Disclosures: **N.B. Kothari:** None. **W. You:** None. **S.P. Mysore:** None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

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Program #/Poster #: 087.09/HHH52

Topic: H.02. Human Cognition and Behavior

Support: ERC-2013-ADG "Perceptual Awareness" Grant

Title: Endogenous attention selectively modulates reaction time and N1 components to unseen stimuli in hemianopic patients

Authors: *J. SANCHEZ LOPEZ, C. A. PEDERSINI, S. SAVAZZI, C. A. MARZI
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Abstract: Previous behavioral studies have shown that in hemianopic patients attention toward the blind hemifield can selectively enhance the response to unseen stimuli. In the present study we assessed the behavioral and electroencephalographic (EEG) modulation produced by implicit spatial visual attention toward a portion of the blind (or sighted) hemifield of five chronic hemianopic patients (age range: 47-75 years old). The task employed a central cue to orient attention toward the to be attended field quadrant. Participants were asked to discriminate, in a forced-choice task, the orientation of a 4 degrees black and white flickering grating. On each block of trials the stimulus could appear always in the same right or left hemifield. However, attention was cued in an upper or a lower quadrant of a given hemifield. Trials could be valid (stimulus presented in the cued quadrant) or invalid (stimulus presented in the uncued quadrant). Classical P1 and N1 attentional event-related potentials (ERPs) components were analyzed. Behavioral results showed significant faster reaction time (RT) for the valid than the invalid condition in both blind and sighted fields while no differences in accuracy were observed. As to ERPs in the blind hemifield, while there was no reliable attention effect for P1, we found a significantly higher amplitude in the valid than in the invalid condition for the different types of N1; namely, contralateral posterior (180-200 ms), parietal (140-180 ms) and fronto-central (120-160 ms). No significant attention effect was found for the sighted hemifield. Stepwise regressions were performed using as predictor the N1 amplitude difference between the valid and invalid condition, and as dependent variable the difference in RT between valid and invalid condition for stimuli presented in the blind hemifield. Results of the regressions showed that the amplitude difference of contralateral posterior, central and ipsilateral anterior electrodes positively predict the RT difference. These results support previous hypotheses about the functional independence of the classical P1 and N1 attentional components. We suggest that the N1 complex plays an important role in the early unconscious sensory gain control of visual attentional processing by recruiting frontal, parietal and visual extrastriate cortical areas. This effect, however, does not enable access to perceptual awareness, even though increases speed of

response. On a more general ground it is possible to conclude that the above results confirm the idea that while consciousness requires attention, attention can operate without perceptual awareness.

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Poster

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Program #/Poster #: 087.10/HHH53

Topic: H.02. Human Cognition and Behavior

Support: ESRC-industry (Toyota, Europe) co funded studentship, UK

Title: Attention modulates cerebral metabolism in the visual cortex

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Abstract: Previous neuroimaging research demonstrated reduced neural responses to unattended stimuli when the attended tasks involve high (vs. low) perceptual load (e.g. conjunction vs. feature search), resulting in the subjective experience of ‘inattention blindness’. Load theory of attention explains these effects within a limited-capacity model. However, our understanding of the physiology underlying these load modulations is limited. We aimed to clarify the physiological correlates of these effects by linking them to cerebral oxygen metabolism that underlies changes in neural firing rates. fMRI research cannot directly inform about cerebral metabolism, since the BOLD response is determined by a complex interplay of cerebral blood flow, blood volume, as well as oxygen metabolism, all of which are driven by different aspects of neural activity. Here we hypothesise that cerebral oxygen metabolism related to an unattended stimulus will be reduced with increased perceptual load in an attended task. To test our hypothesis we used a novel neuroimaging technique, broadband functional near-infrared spectroscopy, that allowed us to monitor redox state changes of cytochrome c oxidase (oxCCO), a mitochondrial enzyme indicative of cellular oxygen metabolism. During our task, participants (n = 16) attended to a rapid stream of crosses and responded to either colour (low load) or colour and orientation combinations (high load), while ignoring a surrounding, flickering checkerboard distractor, present on half of the trials. The oxCCO changes were recorded in 16 channels spread across the occipital cortex. These were grouped into 5 regions of interest based on their MNI coordinates. Metabolic activity related to the presence (vs. absence) of the distractor was significantly reduced in conditions of high (vs. low) perceptual load in the medial occipital lobe

and the right middle occipital gyrus. These findings show that the load-induced attentional modulations of the visual cortex response directly impact the levels of neural oxygen metabolism that underlie changes in neural firing rates.

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Poster

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Topic: H.02. Human Cognition and Behavior

Support: AXA Research Fund (“Neuroergonomics for flight safety” Chair program)

Title: Perceptual performance resulting from inattentive deafness is predicted by pre-stimulus phase relationship of neural oscillations recorded by electroencephalography in real-world situation

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Abstract: The phase of neural oscillations prior to stimulus onset has been identified to play a role in attention and perceptual processes related to future performance. In this study we investigate the phenomena of inattentive deafness, which is defined as a failure to hear otherwise audible sounds (e.g. alarms) that often occurs during high workload situations. The goal is to train a classifier, using machine-learning techniques, to predict whether an alarm presented in the future will be heard and responded to or missed. Our experiment was carried out in real world conditions in which 13 pilots served as participants. The task for the pilot was to press a button when an alarm sound was presented through the headset. There was also a distractor sound that was presented that the pilot was not to respond to (distractor 80%, alarm 20% of presentations). The flight instructor would initiate several scenarios to increase piloting workload with the goal of inducing occurrence of inattentive deafness including diversion of flight course, inflight engine failure, off field landing, and low-altitude circuit patterns. The Cognionics 64 channel dry wireless EEG system was used to record brain activity. The signals were processed by band pass filtering 1 to 30 Hz, automatic channel rejection, automatic subspace reconstruction, and independent component analysis. Independent components consisting of artifacts were removed and the remaining projected to the electrodes. Morlet wavelet analysis was conducted over trials from 1 second before stimulus onset up to the point of stimulus onset at electrode Cz. The phase values at frequencies 6, 9, and 12 Hz from approximately -550 to -470 ms pre-stimulus onset (8 samples evenly spaced across the time

range) were used as features to train the sparse logistic regression classifier using randomly selected equal number of hit and miss trials (100 random iterations). A leave-two-out cross-validation procedure (one hit one miss) was used for evaluation. Classification performance was greater than chance ($p < 0.05$) for 12 of the 13 participants determined by random permutation testing (Mean Accuracy = 73.6%, SE = 1.7, ranging from 59.1% to 81.7%). Using only one frequency reduced the classification to chance performance (Mean Accuracy = 57.6%, SE = 1.8). These results demonstrate that the relationship between phase at various frequencies in time can be used to predict future auditory perceptual performance and may be a neural signature of inattentive deafness and more generally of focused and divided attention under high workload. These results pave the way for the implementation of neuroergonomic technology for adaptive “alarm” presentation.

Disclosures: **D.E. Callan:** None. **T. Vandebrouck:** None. **F. Dehais:** None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

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Topic: H.02. Human Cognition and Behavior

Support: Research Grant no. B32F15000700001 (Ricerca di Base - UNIVR)

Title: Probing the neural mechanisms for distractor filtering and their history-contingent modulation by means of TMS

Authors: C. LEGA¹, O. FERRANTE¹, *E. SANTANDREA¹, F. MARINI², L. CATTANEO¹, L. CHELAZZI¹

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Abstract: In visual search, the presence of a highly salient, singleton distractor interferes with selective processing of the target. This is partly due to the unwanted attentional shift to the salient stimulus, the so-called attentional capture effect, resulting in a measurable cost in performance. The stimulus-driven mechanisms mediating capture are antagonized by goal-driven mechanisms, which on the one hand maintain focus on the sought target while on the other attempt to suppress distractor processing. However, attentional priority is determined not only by goal-directed and stimulus-driven selection, but also by traces of trial history (i.e. the cost of distractor is higher when there was no distractor on the previous trial, compared to when there was one). Lately, there has been growing interest toward the neural mechanisms supporting singleton capture, as well as those responsible for distractor suppression. Although neuroimaging and lesion data converge to indicate a key role of parietal and frontal-prefrontal regions in dealing with visual distractors, their respective role and any hemispheric specialization are still a

matter of debate. Here we used transcranial magnetic stimulation (TMS) to shed light on the possible causal role of two key regions of the dorsal attention network in mediating attentional capture by a salient singleton distractor. Participants were required to discriminate the direction of a target arrow while ignoring a task-irrelevant salient distractor, when present. Immediately after display presentation, TMS was delivered either to the Intraparietal Sulcus (IPS) or the Frontal Eye Field (FEF) on either side of the brain. Compared to a suitable sham condition, TMS over the right FEF reliably reduced the cost engendered by the salient distractor, irrespective of the visual hemifield of target and distractor presentation. We found comparable but weaker effects following right IPS stimulation. These effects were not obtained with TMS stimulation of either site in the left hemisphere. Crucially, the decrease in RT interference from the distractor interacted with the contingent trial history: The beneficial effects of right FEF and right IPS stimulation were greater when there was no distractor on the previous trial relative to when there was one, suggesting a role of TMS in promoting reactive mechanisms for filtering distracting information. These findings provide direct evidence that the right fronto-parietal network houses key mechanisms to limit interference from an irrelevant but attention-grabbing distractor, and further confirm previous evidence of right-hemisphere dominance at least in some forms of attention control.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

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Topic: H.02. Human Cognition and Behavior

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Title: Modulation of parietal alpha power reflects contributions of pitch cues to auditory spatial selective attention

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¹Biomed. Engin., ²Boston Univ., Boston, MA

Abstract: In order to navigate complex scenes, an individual must select target stimuli while suppressing distractors. If the location of the target is known, this can be performed using top-down spatial attention. Neural correlates of spatial attention have been found using electroencephalography (EEG), namely through measurement of event-related potentials (ERP) and alpha (8-14 Hz) power. Increased ERP amplitudes from auditory cortex reflect enhancement of stimuli in the attended location. Increased parietal alpha power ipsilateral to the attended

location is associated with suppression of distractors in the ignored location. While alpha oscillations have been studied extensively in vision, their role in auditory spatial attention is less clear. Furthermore, top-down spatial attention may not persist over the course of an auditory stream if pitch also differentiates target from distractors. We recorded EEG while subjects performed an auditory spatial attention task. Three melodies were presented simultaneously from different directions—left, right, and center—using interaural time differences of $-100\ \mu\text{s}$, $+100\ \mu\text{s}$, and $0\ \mu\text{s}$, respectively. Notes in each melody changed pitch over time, with contours that were rising, falling, or zigzagging. Subjects were cued to attend either the left or right melody and report its pitch contour. The center melody was always ignored. Experimental blocks alternated between two conditions that differed in the pitch separation of the competing melodies: one where the separation was large (~ 10 semitones) and one where it was small (~ 1 semitone). Passive trials, in which subjects ignored all stimuli and withheld a response, were also included. N1 amplitudes and alpha power were measured from the recorded EEG. In frontocentral sensors, N1s for a given note were larger when the note was attended than when it was ignored. Alpha power over parietal sensors varied with spatial attention focus. Compared to the passive condition, alpha power was larger in both left and right parietal sensors when subjects were cued to attend the left melody; when subjects were cued to attend the right, alpha power was larger over right parietal sensors. Importantly, while spatial attention focus changed alpha lateralization similarly in the two pitch conditions, this modulation was stronger when pitch differences were small. These results suggest that alpha modulation reflects suppression during auditory spatial selective attention. When pitch cues are strong, parietal alpha modulation is weak, likely reflecting the fact that pitch differences can be used to help focus attention.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: 087.14/HHH57

Topic: H.02. Human Cognition and Behavior

Title: Mapping the human attention spotlight with multifocal MEG

Authors: ***I. KURKI**¹, **A. HYVÄRINEN**^{3,2}, **L. HENRIKSSON**^{4,5}

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Abstract: Magnetoencephalography (MEG) is a high time resolution brain imaging technique that has great potential in studying dynamics of brain mechanisms, such as visual attention in humans. However, it is commonly thought that the spatial resolution of MEG is severely limited.

Here, we used a multifocal stimulus technique to characterize how stimulus evoked MEG responses are modulated by spatial attention to a certain location in the visual field. The stimulus (radius 12 degrees) consisted of 24 checkerboard patches on 3 concentric rings. One experiment run consisted of 469 trials and lasted 125 seconds. In every trial, each patch was either on or off, controlled by linearly independent sequences. The colour of two target patches at left and right diagonal locations in the lower visual field and at the fixation mark was slightly modulated in 1/10 of the trials. Human observers (N=12) kept their gaze at the central fixation mark while attending to cued target. The task was to detect the colour change at the left target patch, at the right target patch, or at the fixation. Seven experimental runs were collected for each task. Eye tracker was used to monitor the fixation. Evoked magnetic fields were recorded using a 306-channel neuromagnetometer (Elekta Neuromag). General linear model was applied to estimate the stimulus evoked MEG response for every visual field location (stimulus patch) and MEG channel. Machine learning techniques were then used to find channels and locations that are most sensitive to spatial attention related changes. MEG responses showed reasonably good signal-to-noise ratio to every stimulus patch. Thus, rather good spatial resolution can be achieved. Attentional modulation was present from the first MEG response peak, at about 75 milliseconds (ms) post stimulus and up to 400 ms. This modulation was initially spread out in space over several visual field locations but later became very specific to the target location at the later part of the evoked response. Thus, sophisticated signal analysis methods can considerably increase the spatial resolution of MEG, and reveal spatially specific dynamics of attentional processing in humans.

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Poster

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Program #/Poster #: 087.15/HHH58

Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (81771407, 61533006 and 81471653)

Title: Disruption of functional connectivity among subcortical arousal system and cortical network in temporal lobe epilepsy

Authors: *R. LI¹, D. LIU², L. WANG¹, D. LIU⁴, H. CHEN¹, B. XIAO³, L. FENG³

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Abstract: Abstract

Temporal lobe epilepsy (TLE) is a common and debilitating neurological disorder which is characterized by seizures that frequently originate in temporal lobe, such as the hippocampus and the amygdala. However, it remains unclear why responsiveness can be impaired during focal temporal lobe seizures and it is still lacking to directly investigate cerebral cortical and subcortical network changes in human patients with consciousness-impairing seizures. In the present study, to investigate the functional connectivity changes and altered information flow between subcortical arousal system and cortical network in temporal lobe epilepsy (TLE) with consciousness-impairing seizures, we adopted functional connectivity density (FCD) mapping to determine whether there were local or distant functional connectivity changes in TLE patients with impaired awareness and utilized Granger causality analysis (GCA) to further assess the direction and magnitude of causal influence among the altered brain network. Our result showed that TLE patients showed increased local functional connectivity in several subcortical arousal structures ($P < 0.05$, FDR corrected). GCA analysis revealed that causal effects among these regions in patients were significantly sparser than in controls ($P < 0.05$, uncorrected). These findings suggest that consciousness-impairing seizures in TLE are associated with functional alterations and disruption of information process among subcortical arousal system and cortical regions. Understanding the functional networks and innervation pathway involved in TLE can provide insights into mechanism underlying seizure-related loss of consciousness.

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Title: Electrical stimulation over the posterior parietal cortex alters the distribution of attentional priority maps in human visual cortex

Authors: *S. WANG, S. ITTHIPURIPAT, B. CORREIA, G. WOODMAN

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Abstract: Given recent demonstrations that early visual processing can be modulated with transcranial direct current stimulation (tDCS) over human posterior parietal cortex (PPC), it seems logical to propose that this warping of the visual field might also warp how visuospatial attention is distributed across the visual field. We tested this proposal in the current study using unilateral tDCS to PPC before we recorded electroencephalography (EEG) and collected psychophysical data. Subjects performed two different visual tasks each day after undergoing a sham procedure on one day and left or right PPC tDCS on the other day delivered using a double-blind procedure. Hemisphere and order of stimulation were counterbalanced across subjects. After active or sham stimulation, participants completed the attend-fixation and attend-stimulus tasks while we recorded their EEG. In the attend-fixation task, they detected a contrast dimming at a central fixation, while ignoring a checkerboard stimulus of 50% contrast, appearing randomly at six locations along the horizontal meridian. In the attend-stimulus task, the stimulus display was identical, but subjects covertly attended to the six stimulus locations to detect a contrast dimming at the stimulus location. Behaviorally, we found that active stimulation induced an asymmetry in psychophysical contrast thresholds measured across the attended stimuli, suggesting a shift of attention to the visual field contralateral to the stimulated hemisphere. The electrophysiological findings supported this interpretation with stimulation enhancing the P1 attentional modulations of visual stimuli contralateral to the stimulated hemisphere. Taken together, our results show that the anodal tDCS over the PPC can alter the distribution of visuospatial attention.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.17/HHH60

Topic: H.02. Human Cognition and Behavior

Support: Australian Research Council Discovery Project 170101840
Australia Research Council Future Fellowship FT170100105
Medical Research Council (UK) intramural funding SUAG/035/RG91365

Title: Linking adaptive neural responses to behaviour using magnetoencephalography

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Abstract: The human brain is extremely flexible and capable of rapidly selecting relevant information in accordance with task goals. Functional magnetic resonance imaging (fMRI) studies have shown that multiple demand (MD) regions in frontoparietal cortex flexibly represent relevant task information such as task rules (e.g., Woolgar et al., 2015) and stimulus features (e.g., Jackson et al., 2017). The time course of these adaptive processes are still unclear. One pertinent question is when and how task-related neural activity relates to behaviour. In this experiment, we used magnetoencephalography (MEG) and pattern classification techniques to investigate the temporal dynamics of goal-directed behaviour. Participants responded to the location of a target stimulus using one of two response-mapping rules. The target stimulus appeared in one of four locations, each associated with a different response depending on the rule. To investigate the relationship between the brain representations of stimulus and rule information and behaviour, the task was designed to be difficult from two perspectives: 1. The stimulus locations were perceptually confusable, and 2. the response mapping rules were difficult. Importantly, the rules were designed so that incorrect trials could be classified as stimulus errors (i.e. correct rule applied to the incorrect location) or rule errors (i.e. incorrect rule applied to the correct location). As expected, time-resolved multivariate pattern analysis revealed different dynamics for perceptual and rule-related processes. For correct trials, stimulus position could be decoded shortly after stimulus onset, consistent with early retinotopic visual processing. Rule decoding emerged later, consistent with higher-level cognitive control processes. Analyses time-locked to the response revealed that position and rule decoding slowly increased until the response was made. Crucially, when participants made a stimulus error, patterns of activity preceding the response resembled the *incorrect* stimulus position, indicating that the brain representation of stimulus location was associated with the response. These results provide important evidence about the temporal dynamics of stimulus and rule processing. Overall, it is clear that brain representations measured using MEG can provide a great deal of insight into the relationship between neural activity and behaviour.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.18/HHH61

Topic: H.02. Human Cognition and Behavior

Support: CIHR Doctoral Award to SLR
NSERC Discovery Grant to GRT

Title: Self-reported media use is associated with altered brain activity during sustained attention

Authors: ***S. LEMIRE-RODGER**¹, E. R. CONNELL¹, W. D. STEVENS², G. R. TURNER³
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Abstract: Recent research on the use of technology during in-class or at-home study time has highlighted the negative impact of active social media use on learning and academic success. “Multi-tasking” has become ubiquitous in modern lecture halls, and digital distraction is a growing concern not only for college students, but also for technologically connected users in many contexts. (e.g. Sana, Weston & Cepeda, 2013). We know sustained attention is critically dependent on interactions between frontal, parietal, and subcortical brain regions (Lawrence et al., 2006), but how these interactions are associated with social media use is poorly understood. We set out to determine if self-reported social media use, particularly the concurrent use of social media while performing other tasks, is associated with brain function during a sustained attention task. Young adults (N=20, 7 male, $M_{age} = 19.43$) completed a questionnaire about their social media use that included a section on divided attention (how often they used social media while engaging in other activities), they then underwent fMRI scanning while they completed a modified version of the Conjunctive Continuous Performance Task. In this task, participants were presented with number-letter pairs and asked to press 1 for all pairs, with the exception of a randomly selected target pair, for which they were instructed to press 2. The 10-minute task was broken down into 5 epochs, each modeled with a series of consecutive 12-second blocks. The data were then analyzed using a multivariate, behavioral Partial Least Squares approach, identifying correlations between covariance patterns of brain activity over the different epochs and scores on the social media and multi-tasking survey. A significant latent-variable characterizing correlations between brain activity patterns and social media scores emerged ($p < .001$). Lower self-reported scores on the survey were associated with a covarying pattern of brain activity in frontal control and visual attention regions, including the inferior parietal lobule, middle frontal gyrus, medial superior prefrontal cortex, and precuneus. Three areas were associated with higher self-reported divided attention scores, particularly during the earliest and latest time periods of the task: the left superior medial frontal gyrus, bilateral posterior cingulate, and the left posterior aspect of the thalamus. These findings provide evidence that regular use of social media across different contexts is related to altered neural mechanisms supporting sustained attention. Further research is needed to establish the directionality of this relationship.

Disclosures: **S. Lemire-Rodger:** None. **E.R. Connell:** None. **W.D. Stevens:** None. **G.R. Turner:** None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.19/III1

Topic: H.02. Human Cognition and Behavior

Title: Can meditation improve attention in older adults at risk for falls?

Authors: *S. FORD¹, L. S. NAGAMATSU²

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Abstract: Falls in older adults are a major health care concern given the resulting injuries and medical costs. Previous literature suggests that recurrent falls among older adults are not merely accidents, but rather caused by intrinsic factors. One such factor that has been linked to falls is poor attention. A strategy that has been shown to improve attention in other populations, and more recently in older adults, is meditation. Meditation can be defined as regulation of the self and bringing awareness and focus to the present moment. Therefore, our current study examined whether using meditation training in an older adult population with a history of recurrent falls would improve their attention. We conducted a four-week intervention where 60 participants were randomly assigned to either a: 1) focused attention (FA) meditation condition, or 2) an acoustic music listening (control) condition three times a week. Both groups were recruited from independent-living retirement homes and met in their community for the study sessions in clusters of 4-6 people. All participants were encouraged to practice either meditation or listening to calming music on their own in between sessions. Before and after the four-week intervention we assessed attention using: 1) the Sustained Attention to Response Task (SART) which measured reaction time and accuracy, and 2) EEG during resting state where we measured individual alpha peak frequency (iAPF). The SART measures a participant's ability to sustain attention over time, and iAPF measures the participant's highest alpha frequency brain waves. Our results show a significant improvement in SART performance indicated by an increase in accuracy and decrease in reaction time, as well as an increase in iAPF in the FA meditation group compared to the control group. The FA meditation group also showed a non-significant trend towards an improvement in overall mobility measured from time 1 to time 2. Mobility was measured by several assessments including the Timed Up and Go Test and the Short Physical Performance Battery. The control (music) group did not show any significant differences across time points. These results suggest that FA meditation can increase attention in older adults, possibly decreasing their risk of falls and reducing falls-related injuries. Future research should employ a longer intervention to investigate if these changes in mobility can be strengthened with more meditation practice. In conclusion, the use of focused attention meditation in older adults may provide an accessible intervention to improve mobility, and therefore independence and quality of life.

Disclosures: S. Ford: None. L.S. Nagamatsu: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.20/III2

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust-DBT India Alliance

Title: The posterior parietal cortex mediates spatial bias reorienting during visual attention

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Abstract: Spatial attention enables us to select stimuli at particular, behaviorally relevant, locations for enhanced sensory processing and decision-making. Attention operates through one or both of two mechanisms: i) by enhancing perceptual sensitivity, or enhancing the quality of sensory information processing of the selected target, and ii) by enhancing decisional bias, or enhancing the weight afforded to the selected target during decisions. It remains unknown if sensitivity and bias mechanisms are mediated by common or distinct neural mechanisms [1]. We addressed this question with a combination of model-based psychophysics and transcranial magnetic stimulation. First, we tested human observers (n=30) on a top-down attention task, involving a five-alternative change detection paradigm. We fit a recently developed multidimensional signal detection model [1] - the m-ADC model - to quantify sensitivity and bias from psychophysical performance. The model fit behavioral data robustly and revealed dissociable effects of cueing on sensitivity and bias. While bias varied in a graded pattern reflecting cue validities across locations, sensitivity varied in an 'all or none' manner, being highest at the cued location but not significantly different among the uncued locations. Sensitivity and bias modulations induced by cueing were uncorrelated across subjects. Moreover, bias rather than sensitivity was robustly affected key metrics of reaction times and optimal decisions. Next, we investigated the role of the right posterior parietal cortex, a key node of the frontoparietal attentional network, in modulating sensitivity and bias. For this, we applied continuous theta burst stimulation (cTBS), a protocol that transiently suppresses neural activity [2], to the right PPC. Human observers (n=25) performed a spatially cued, change detection task, and sensitivity and bias were quantified with the m-ADC model. cTBS of the right PPC produced no significant effects on sensitivity but produced a robust reduction in bias toward the uncued location relative to the cued location. Taken together, our results indicate that sensitivity and bias are mediated by distinct neural mechanisms and implicate the right PPC, specifically, in reorienting decisional bias from the attended to the unattended location.

[1] Sridharan D, Steinmetz NA, Moore T, Knudsen EI (2017) Does the superior colliculus control perceptual sensitivity or choice bias during attention? Evidence from a multialternative

decision framework. *J Neurosci* 37(3):480-511.

[2] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, & Rothwell JC (2005) Theta burst stimulation of the human motor cortex. *Neuron*, 45(2):201-206.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.21/III3

Topic: H.02. Human Cognition and Behavior

Support: Supported by the Institute for Collaborative Biotechnologies through contract W911NF-09-D-001 from the U.S. Army Research Office

Title: Fear and loathing in visual search under stress

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Abstract: Phobias not only increase involuntary attention capture by feared stimuli, but also by non-feared salient stimuli when the presence of a salient feared stimulus is possible. Thus, the stress induced by the anticipation of a feared stimulus affects the priority of factors other than fear, i.e. salience. Stress generally increases involuntary attention capture by emotional stimuli, but it is unclear whether the presence of feared stimuli affects priority of non-feared salient stimuli as with phobias. Participants (n = 14) completed a visual search task that could include feared (spider) and neutral (butterfly) salient distracters in a baseline session, and then again in stress and control sessions. Stress was induced using the cold pressor (feet immersed in ice water for 90 s; warm water for control), which evokes a cortisol response, prior to and following the visual search task. Salient distracters captured attention under all conditions, such that reaction times (RT) were slower when a salient distracter was present than when absent. When the salient distracter was equally likely to be feared or neutral within a block of trials capture was equivalent for feared and neutral distracters ($M_{\Delta} = 14$ ms for both, p 's < .01), and there was no effect of stress state. However, in blocks where the salient distracter was predictably feared or neutral there was a three-way interaction between stress states (baseline, stress, control), valence (feared or neutral), and the presence or absence of a salient distracter on RT ($F(2,26) = 4.23$, $p = .026$, $\eta^2 = .25$). Under the stress condition feared distracters captured attention ($M_{\Delta} = 24$ ms, $p = .008$), but neutral did not ($M_{\Delta} = 12$ ms, $p = .102$). The opposite was observed in the control condition, where the neutral distracters captured attention ($M_{\Delta} = 27$ ms, $p < .001$), but feared did

not ($M_{\Delta} = 2$ ms, $p = .611$). Both feared ($M_{\Delta} = 19$ ms) and neutral ($M_{\Delta} = 28$ ms) distracters captured attention in the baseline (p 's $< .02$). Attention capture was accompanied by impaired target processing ($n = 9/14$) as indicated by the magnitude of the N2pc effect (ipsi $<$ contra to target), which was smaller in the presence of a feared salient distracter than a neutral one under stress ($t(8) = 2.44$, $p = .041$, $M_{\Delta} = 0.716 \mu V^2$). No difference was observed in the control condition ($t < 1$, $p = .640$, $M_{\Delta} = 0.261 \mu V^2$). These results indicate that stress, induced via an aversive experience, influences priority of not only salient feared information, but also priority of other salient information, resulting in relatively impaired target processing in the presence of feared stimuli, and that these effects are moderated by expectations of the probability that a feared or non-feared salient stimulus will appear.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.22/III4

Topic: H.02. Human Cognition and Behavior

Support: NIH grant R37NS21135 (RTK)
McDonnell Foundation (RTK)
Research Council of Norway 240389/F20 (AKS/TE)

Title: Large-scale network interactions underlying internally directed attention

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Abstract: Humans spend up to half of their waking hours engaged in internally directed processes, yet how the brain facilitates these internal states remains a mystery. While recent neuroimaging evidence has implicated both the default mode network and fronto-parietal control network in internally directed processes, the underlying neural mechanism is still largely unknown. To address this issue, we recorded intracranial EEG activity in patients undergoing presurgical monitoring for refractory epilepsy who were implanted with subdural and/or depth electrodes. Patients performed an attention task wherein half the time, they had to detect target tones (i.e. external condition); the other half of the time, they were instructed to think about whatever comes to mind and ignore all the tones (i.e. internal condition). We correlated theta

power between electrode pairs located in the default mode network or the fronto-parietal control network, which were then examined as a function of condition across patients. We found increased correlation between the default mode network and the fronto-parietal control network during the internal relative to external attention conditions. These results indicate that enhanced spatiotemporal integration of information between the default mode network and the fronto-parietal control network is one potential mechanism in facilitating internally directed attention.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.23/III5

Topic: H.02. Human Cognition and Behavior

Support: Supported by the Institute for Collaborative Biotechnologies through contract W911NF-09-D-0001 from the US Army Research Office

Title: Illusory contour neural coding in human cortex is modulated by selective attention

Authors: ***T. W. BULLOCK**^{1,2}, **A. STROM**¹, **M. MACLEAN**^{1,2}, **B. GIESBRECHT**^{1,2}
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Abstract: The Kanizsa figure is a well-known example of an illusory contour (IC), where induced borders are perceived despite their physical absence in the scene. While there is ample evidence that ICs are coded by populations of neurons in visual cortex, there is some question about whether these neural codes are generated automatically and are independent of attentional demands. To investigate this question, participants ($n=26$) were presented with inducers that either formed an IC or did not, under two different attention conditions. More specifically, participants viewed 12 black inducers arranged equidistantly in an imaginary circle around a dark gray fixation circle. The inducers oscillated on and off at 30 Hz while a stream of letters was presented at fixation (7.5 Hz). On each trial (800 ms duration), four inducers rotated from their default position (facing outwards) to form either an illusory bar (IC-present) or no bar (IC-absent). A different combination of inducers rotated on each trial, creating the illusion of a bar moving between six unique orientations in the IC-present configuration. Participants fixated on the central fixation circle and were required to either monitor the inducers for a rare ($p=.11$) contrast change in one of the rotated inducers (attend-inducer) or the presence of a letter "X" (attend-letters) and indicate the presence of a target with a button press. The conditions were presented in a blocked full factorial design while recording EEG at 64 scalp locations.

Behavioral performance was equivalent across all conditions (~80% hits, $p > .05$). We used an inverted encoding modeling technique to estimate orientation-selective tuning functions (TFs) from spatially distributed activity measured at the stimulation frequency (30 Hz) across the scalp during each trial. TFs were folded at the center (around the peak) and the slope of the folded function was calculated and used to compare between conditions. When evoked activity (i.e. activity phase-locked to the inducer onset) was entered into the model, we observed greater slope in the IC-present vs. IC-absent conditions ($p < .05$) and no interaction with the direction of attention ($p > .05$). When total activity (i.e. activity regardless of phase) was entered into the model, we observed greater slope in the IC-present vs. IC-absent attend-inducer conditions ($p < .05$) but no difference in slope between the attend-letters conditions ($p > .05$). Together, these results demonstrate that it is possible to estimate orientation-selective neural coding profiles from EEG data acquired from participants viewing Kanizsa figures, and that these patterns of activity can be modulated by the focus of attention.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.24/III6

Topic: H.02. Human Cognition and Behavior

Title: How involuntary and voluntary attention interact: Examining neural biasing mechanisms during the cue-target interval

Authors: *J. M. KEEFE, V. S. STÖRMER
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Abstract: Spatial attention can enhance perceptual processing regardless of whether it is deployed involuntarily (e.g., when captured by a salient event in the environment) or voluntarily (e.g., through task instructions). While many studies have focused on the perceptual consequences of involuntary and voluntary attention, less is known about the neural mechanisms giving rise to these effects. Here, we utilized EEG to compare neural activity elicited by spatial attention cues in an involuntary and voluntary attention task within the same participants. We used a cross-modal cueing paradigm in which a noise burst was presented from one of two speakers placed on the left and right side of a computer monitor, followed by a visual target (tilted Gabor patch) at one of these peripheral locations. In both tasks, participants were asked to discriminate the tilt direction of the visual target. In the involuntary cueing task, the sound was randomly played on the left or right side 130 ms prior to the target and did not provide any information about the location of the target. In the voluntary cueing task, the sound was presented 1,000 ms prior to the target and predicted the target location with 80% validity.

Participants (N=14) were instructed to attend to the cued location in the voluntary attention task and to ignore the sound in the involuntary attention task. Consistent with previous research, participants showed higher target discrimination accuracy for validly versus invalidly cued targets in both the involuntary ($p < 0.001$) and voluntary ($p = 0.002$) attention tasks. Furthermore, we found that the peripheral sound increased neural activity in visual cortex contralateral to the cued side in both tasks, observed as a slow positive deflection over occipital scalp sites ~260-400 ms after cue onset (i.e., auditory-evoked contralateral occipital positivity, ACOP; involuntary task: $p = 0.0003$; voluntary task: $p = 0.003$). This positive deflection was followed by a sustained negativity over parietal-occipital scalp sites (~700-1000 ms after cue onset) only in the voluntary cueing task ($p = 0.014$). This later negativity likely reflects the maintenance of visual-spatial attention at the anticipated target location. Overall, these findings show that a salient, peripheral sound triggers a rapid shift of visual-spatial attention to its location and initially modulates visual-cortical activity regardless of its predictive value. This involuntary component of attention is then followed by sustained component only when the cue carries predictive value.

Disclosures: J.M. Keefe: None. V.S. Störmer: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.25/III7

Topic: H.02. Human Cognition and Behavior

Support: Grant to FD - Fondazione Terzo Pilastro - Roma Italia

Title: Abnormal patterns of α -band EEG asymmetry during preparatory orienting of attention in left spatial neglect

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Abstract: EEG studies monitoring preparatory orienting of spatial attention ahead of the occurrence of visual targets in the left or right side of space, have pointed out decreased alpha-activity over the hemisphere contralateral to the attended side of space and increased alpha over the ipsilateral hemisphere (Thut et al., 2006). Decrease and increase in alpha activity reflect enhanced cortical excitability facilitating processing of visual inputs at attended spatial positions and active inhibition of input arriving from unattended positions, respectively. Most important, it was pointed out that in healthy humans the degree of alpha asymmetry during preparatory orienting predicts faster detection of forthcoming visual targets in the attended side of space

(Thut et al., 2006). Here, we investigated hemispheric asymmetries of alpha activity during cued orienting of attention in right brain damaged patients (RBD) patients with left spatial neglect, who show impaired attentional processing of stimuli in the left side of space, in RBD patients without neglect (N-) and in healthy controls (C). The presence of pathological patterns in the hemispheric distribution of alpha activity during preparatory orienting in N+ patients, can provide a useful diagnostic tool for these patients who suffer poor clinical outcome and cope with longer and socially expensive rehabilitation treatments.

We have found that N+ show pathological enhancement of alpha activity over the damaged right hemisphere, and a corresponding reduction of alpha over the left hemisphere, that is independent from the direction of cued orienting, i.e. leftward, rightward or toward both sides of space. N- patients show a similar though far less enhanced asymmetry. C show a typical reduction of alpha over the hemisphere contralateral to the cued side of space. When compared to N- and C, in N+, the pathological asymmetry of alpha activity during preparatory orienting was matched with a severe drop in the detection of visual targets in the left side of space. In the whole group of patients (N+ and N-) the asymmetry of alpha recorded during the presentation of neutral cues that pointed toward both sides of space was correlated with neglect severity in the line bisection test and with lesion size. The comparative analyses of lesion overlaps in N+ and N- showed three peaks of lesion overlap in N+: one in the white matter of the frontal operculum, one in the anterior segment of the arcuate fasciculus and one in the posterior segment of the arcuate fasciculus.

Reference. Thut et al. (2006). *Journal of Neuroscience*, 26(37), 9494-9502.

Disclosures: S. Lasaponara: None. F. Doricchi: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.26/III8

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant 2R01MH087214-06A1

Title: Covert spatial attention speeds target individuation

Authors: *J. J. FOSTER, E. M. BSALES, E. AWH
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Abstract: Covert spatial attention is thought to enhance both the quality and speed of visual processing at attended locations. However, while an extensive body of work has established that covert attention improves the *quality* of information available to guide a response (for review, see Carrasco, 2011), the evidence that covert attention *speeds* visual processing is lacking.

Behaviorally, it is difficult to test whether covert attention speeds processing because improved discriminability at attended locations can lead to faster responses. Using a speed-accuracy tradeoff procedure, Carrasco and McElree (2001) found that information processing was faster when improved discriminability was accounted for. However, because this method relies on behavioral outputs it is difficult to establish whether attention directly speeded the initial identification of the target, or whether attention enabled more efficient use of that information during subsequent decision stages of processing. To isolate early stages of visual processing, others have tested whether covert attention speeds visual processing by examining the latency of early visually evoked potentials measured with EEG (e.g., the P1 and N1 components). However, the results have been mixed: some studies reported earlier responses, but most found that attention increased the amplitude of evoked potentials without changing their latency. To re-examine this longstanding question, we manipulated whether or not covert attention was deployed to the target location prior to the onset of a search array. In some blocks, a spatial cue indicated the exact location of the forthcoming target, while in other blocks the cue was spatially uninformative. We used ongoing alpha activity to verify the specific locus of covert attention prior to target onset. In line with past work, alpha oscillations precisely tracked the cued location following informative cues, but showed no evidence of spatial orienting following neutral cues. To test whether spatial attention speeds visual processing, we examined the N2pc - an event-related potential that reflects individuation, the segregation of selected items from the background and other items in the display. We reasoned that if covert spatial attention speeds visual processing, then the target-locked N2pc should occur earlier following informative cues than following uninformative cues. In two experiments, we found that the N2pc onset earlier following spatially informative cues. These results demonstrate that spatial precues speed target individuation, providing clear evidence that covert spatial attention can speed perceptual processing.

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Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

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Program #/Poster #: 087.27/III9

Topic: H.02. Human Cognition and Behavior

Support: Duke University - John Templeton Foundation SSNAP Award 48365

Title: Dissociating the effects of affective salience and signal probability on visual attention

Authors: *M. JATIVA, J. H. KRYKLYWY, S. HU, M. RANSOM, J. MARKOVIC, S. FAZELPOUR, R. M. TODD
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Abstract: Recent evidence has shown that both a stimulus' association with punishment and the predictability of its occurrence can influence attentional prioritization. Learning about statistical regularities of the environment serves the goal of predicting frequently occurring events required for action, while guidance of attention by punishment serves the goal of acquiring and holding on to sources of physical danger. The goal of this study was to manipulate and dissociate the influences of affective salience and probability as separate sources of attentional guidance. To disembody the contributions of expectation and emotion as separate sources of attentional guidance, we conducted a signal detection task wherein affective salience is manipulated through classical conditioning, and signal probability - the frequency of a signal appearing in a given location - is explicitly stated. Results were analyzed using traditional signal detection theory and a formal computational model that dissociates these two types of prior information. Preliminary results replicate prior work showing increases in both hit percentage and false alarms with increasing signal probability (Wyart et al., 2012). Furthermore, an increased hit rate for stimuli with high compared to low affective salience was observed. Additional analyses use a reverse-correlation technique to estimate the sensitivity of true and false positives to parametric changes in signal energy. We interpret these findings as evidence for the separate influences of affective salience and expectation on mechanisms of visual attention.

Disclosures: **M. Jativa:** None. **J.H. Kryklywy:** None. **S. Hu:** None. **M. Ransom:** None. **J. Markovic:** None. **S. Fazelpour:** None. **R.M. Todd:** None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.28/III10

Topic: H.02. Human Cognition and Behavior

Support: European Research Council consolidator grant 648480 to SK

Title: Cortical dynamics of auditory attention during mind wandering

Authors: *N. BARASCUD¹, J. SACKUR^{1,2}, S. KOUIDER¹

¹LSCP, Ecole Normale Supérieure, Paris, France; ²École des Hautes Études en Sci. Sociales, Paris, France

Abstract: Background While the propensity of the human mind to wander is well documented, the neural basis of this drift in attention and its relation to behaviour remain poorly understood. Here, we examined whether these periods of “mind wandering” are associated with reduced cortical tracking of the external auditory environment. We used electroencephalography (EEG) and a stimulus decoding model to study single-trial dynamics of attentional tracking of sound in a cocktail-party situation, where subjects were selectively listening to one of two competing

speakers and probed for mind wandering at unexpected moments.

Methods 25 naïve subjects participated in the study. Stimuli were excerpts of two audio books (*Regard sur le monde actuel* by Paul Valéry, and *Discours sur l'Histoire universelle* by Jacques Bossuet), narrated by a female and a male speaker, respectively. Periods of silence longer than 0.5 s were truncated, and all sounds were normalized to have the same root-mean-square intensity. Male and female speech streams were presented in opposite ears (counterbalanced across sessions and subjects). Subjects performed 6 such dichotic listening sessions, as well as 1 diotic (single stream) session of ~10 min each. During each listening session, a probe sound was played at a random interval every 20 to 140 s, asking participants to self-report whether they were attending (*on-task* trials), or mind-wandering (*off-task* trials). In addition to these self-reports, subjects also answered comprehension questions at the end of each listening session.

Results EEG data (64 channels) from all listening sessions were submitted to a decoding model, which predicted stimulus features from brain activity. In accordance with previous findings, we show that attentional selection in a naturalistic dual-speaker environment can be tracked on a single-trial (~10s) basis. Importantly, stream decoding accuracy was significantly lower during mind wandering. Behaviourally, self-reports of mind-wandering correlated with speech comprehension, such that scores were significantly higher when subjects reported being on-task versus off-task. Furthermore, regression analysis showed significant common variance between EEG and behavioural markers of mind wandering, suggesting that both markers reflect a common underlying mental state. Overall, our results suggest that the cortical representation of speech does not simply reflect the external acoustic environment, but instead is strongly modulated the listener's internal state. Ultimately, our approach could provide a useful alternative to self-reports for monitoring attention in real-time.

Disclosures: N. Barascud: None. J. Sackur: None. S. Kouider: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.29/III11

Topic: H.02. Human Cognition and Behavior

Title: Does peripheral target dimension affect precision of saccade planning?

Authors: *A. N. SWANSON¹, W. E. HUDDLESTON²

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Abstract: Understanding how attention modulates signals across the motor system is of fundamental importance to direct the most efficient treatment for syndromes such as hemispatial neglect, often associated with stroke. The presence of neglect post-stroke is a key predictor of

loss of independence, demonstrating the significant impact of attentional dysfunction on overall function. While others have manipulated target size and evaluated saccade accuracy, our focus was on the planning of saccades relative to target dimension. Specifically, we hypothesized that saccade planning would vary based on target size, with less precise saccades occurring towards larger target regions. Healthy participants between the ages of 18 and 50 attended to a stimulus consisting of an RSVP stream of letters and numbers changing at a rate of 125 objects/second, surrounded by a thin circular outline (radius 10 degrees of visual angle) representing clock positions on a circle (actual numbers not present). Every 4 sec a clock location was indicated by a number appearing in the RSVP stream (e.g., 3 = 3:00) while the intervening time was filled with randomly presented letters. An occasional 'X' informed the participant to perform a rapid, yet accurate, saccade to the most recently cued 'clock' location. Participants planned eye movements to each corresponding number around the clock. Monitoring for the go cue ('X') embedded in the central RSVP maintained visuospatial attention centrally while motor attention incremented along the peripheral circle in an attentional drift design. Participants completed 11-14 saccades per each clock cycle, performing saccades to each location four times across the four runs for a total of 96 saccades. All participants performed the task under two conditions in which the thickness of the peripheral ring was modified to vary the necessary preciseness of saccade planning (i.e., a thicker ring would require less precision). Dependent measures included reaction time, reaction time variability, saccade endpoint accuracy, and saccade endpoint variability. Reaction times, and their variability, did not change between the two conditions. However, individual responses to the two conditions varied. Some participants had greater inaccuracy or greater variability in one condition versus the other, highlighting the importance of evaluating individual differences. An understanding of attentional processes involved in the selection of salient information for motor planning may provide a foundation for targeted therapies for individuals with motor attention deficits (e.g., stroke).

Disclosures: A.N. Swanson: None. W.E. Huddleston: None.

Poster

087. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 087.30/III12

Topic: H.02. Human Cognition and Behavior

Support: NCATS CTSA UL1TR001436

Title: Voxel-wise modeling of attention fields in the motor system

Authors: *W. E. HUDDLESTON¹, A. S. GREENBERG², J. MATHIS³, E. A. DEYOE³

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Milwaukee, WI; ²Dept. of Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; ³Dept. of Radiology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Given the ubiquitous influence of attention on multiple sensory, motor and cognitive functions, it is surprising more effort has not been devoted to comparing and contrasting the roles and mechanisms of attention across these different domains. Our focus was on the internal structure of neural maps across modalities. To date, the Puckett-DeYoe attention model, among others, have focused primarily on visual processing, yet by simply substituting the nature of the type of map on which they operate (e.g. saccadic), the same type of computation may occur widely throughout the brain to permit attentional selection and modulation of various sensory *and* motor functions. We hypothesized that similar to visual attention, motor attention related to saccade planning could also be modeled with an attention field that was distinct from the ‘motor’ field. In nine participants, we quantified meso-scale (voxel) attentional modulation within multiple saccadic maps using a previously developed computational model (Puckett & DeYoe 2015) consisting of a local motor action field (pMF), an attentional modulatory field (pAF) whose position, shape and profile were distinct from those of pMFs, and a computational model of pAF/pMF interaction. An attentional drift design was created for saccade planning (motor attention). Subjects visually attended to a centrally presented RSVP letter stream surrounded by a thin circular outline (radius 10 degrees of visual angle) representing clock positions on a circle. Every 4 sec a clock location was indicated by a number appearing in the RSVP stream (e.g., 3 = 3:00), while the intervening time was filled with randomly presented letters. A rarely presented ‘X’ informed the participant to perform a rapid, yet accurate, saccade to the most recently cued ‘clock’ location. The peripheral circular outline was static to avoid sensory transients that might capture attention or introduce confounding sensory signals. Thus, the focus of motor attention (a.k.a. saccade planning) drifted through a saccade target map, modulating the successive locations representing the intended saccade trajectories. Visual attention focused on the central RSVP task containing target location and go cues. The occasional real saccades were brief and random, so their BOLD signals would be distinct from the regular, cyclic saccade motor attention signals and could be separately modeled or excluded. We were, in fact, able to model pMFs and PAFs in separate maps throughout the saccade motor pathway; thereby providing some of the first quantitative, empirical evidence for the general applicability of specific, well defined, attentional modulation across a motor modality.

Disclosures: **W.E. Huddleston:** None. **A.S. Greenberg:** None. **J. Mathis:** None. **E.A. DeYoe:** None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.01/III13

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: HHMI-Simons Fellowship

John Doerr

Open Philanthropy project

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NIH Grant 1R01MH103910

NIH Grant 1RM1HG008525

NIH Grant 1R01MH110932

Title: Expansion microscopy using lipid and protein labels for multimodal structural and functional nanoresolution imaging of brain circuits

Authors: J. KANG, *E. D. KARAGIANNIS, T. SHIN, C.-C. YU, E. COSTA, A. EMENARI, E. S. BOYDEN

MIT, Cambridge, MA

Abstract: J-SK and EDK contributed to this work equally.

Brain functions emerge from the functional interaction of neuronal structures that span many orders of magnitude in spatial scale, from the nanometer scale size and organization of synaptic proteins to the macroscopic wiring of neuronal circuits. Expansion Microscopy (ExM; Science (2015) 347(6221):543-548) enables nanometer resolution imaging across extended 3-D spatial scales through the physical magnification of biological specimens, followed by imaging via conventional, high-speed, diffraction-limited optics. Recently, we developed polymer-anchorable lipid intercalating labels that can bind to plasma membranes (and other lipid membranes) of neurons and other cells. These labels can then be anchored to expandable polymers, and the resultant tissues expanded by ~20-fold, providing sub-15nm resolution, by employing a polymeric strategy that we call iterative expansion microscopy (iExM; Nat Methods (2017) 14(6):593-599). Here we combine such iExM-compatible lipid binding tags with protein labeling (e.g., via antibodies) to assess whether such an integrated toolbox can enable the imaging of key proteins in the context of well-resolved lipid membranes, as would be desired for the imaging of synapses and other key compartments of complexly shaped cells such as neurons. We validate this toolbox method via joint labeling of co-localized protein and lipid domains, i.e. by labeling for protein markers of cellular organelles such as mitochondria, endoplasmic reticulum, and golgi apparatus, and comparing the resultant protein maps with simultaneously imaged lipid labels staining the same organelles. We also stain for synaptic protein markers, and compare the resulting protein maps to the lipid labels simultaneously imaged on the same synapses, which may point to novel strategies for neural connectomics. In this way, by merging protein and lipid stains in the context of iterative expansion microscopy, we aim to enable the large-scale reconstruction of structural and molecular information in brain circuits with nanometer resolution.

Disclosures: J. Kang: None. E.D. Karagiannis: None. T. Shin: None. C. Yu: None. E. Costa: None. A. Emenari: None. E.S. Boyden: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.02/III14

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1R01NS102727

NIH 1R01EB024261

John Doerr

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Open Philanthropy Project

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IARPA D16PC00008

Title: Expansion microscopy of *C. elegans* enables whole-organism *in situ* analysis with nanoscale spatial resolution

Authors: *C.-C. YU¹, N. BARRY², K. D. PIATKEVICH², S. ASANO², G. HUYNH², A. KAZATSKAYA⁶, I. NECHIPURENKO⁶, E. CRONIN⁷, I. SKVORTSOV⁷, Z. TANVIR⁷, S. W. FLAVELL^{3,4}, P. SENGUPTA⁶, G. HASPEL⁷, M. B. GOODMAN⁸, E. S. BOYDEN^{1,2,3,5}
¹Dept. of Biol. Engin., ²Media Lab., ³Dept. of Brain and Cognitive Sci., ⁴Picower Inst. for Learning & Memory, ⁵McGovern Inst. for Brain Res., MIT, Cambridge, MA; ⁶Dept. of Biol. and Natl. Ctr. for Behavioral Genomics, Brandeis Univ., Waltham, MA; ⁷Federated Dept. of Biol. Sci. and the Brain Res. Inst., NJIT and Rutgers University-Newark, Newark, NJ; ⁸Mol. and Cell. Physiol., Stanford Univ., Stanford, CA

Abstract: In order to reveal principles of neural circuit operation, it would be useful to examine molecular profiles of neurons, structural connectivity between neurons, and dynamics of neuronal signaling, ideally throughout an animal's entire nervous system, and to compare such integrated information to the emergent behavior of the animal. The nematode *Caenorhabditis elegans* is well suited for such multi-domain analysis, due to its small nervous system with known connectivity, and the possibility of imaging neural dynamics throughout its nervous system at high speeds. Recently we developed expansion microscopy (ExM, Science (2015) 347(6221):543-548), which physically expands biological systems via polymer embedding and specimen swelling, enabling nanoscale resolution imaging of extended 3-D systems like neural circuits. However, *C. elegans* possesses a tough cuticle, which is a layer of exoskeleton impermeable to reagents including antibodies and RNA hybridization probes, and which can resist expansion. We have now developed a method to physically expand fixed *C. elegans* tissues and organisms with high isotropy. This method, named Expansion of *C. elegans* (ExCel), combines multiple molecular-retention strategies and allows simultaneous readout of fluorescent

proteins, RNAs, DNA, and general morphological structures of the nematode at a resolution of ~100 nm for ~4x expansion factor. ExCel is also compatible with iterative expansion microscopy (iExM, Nature Methods (2017) 14:593-599), which results in a 20x expansion factor, and enables visualization of fine morphological features with resolutions up to ~25 nm. We demonstrate the utility of ExCel in facilitating neuronal connectomic analysis and single-neuron resolution mRNA detection. Thus, ExCel is a robust method for in situ analyses of the *C. elegans* nervous system at sub-cellular resolution, which can be useful for generating new hypotheses to be tested in systems neuroscience, and to provide co-registered multimodal data for the generation of new computational models.

Disclosures: C. Yu: None. N. Barry: None. K.D. Piatkevich: None. S. Asano: None. G. Huynh: None. A. Kazatskaya: None. I. Nechipurenko: None. E. Cronin: None. I. Skvortsov: None. Z. Tanvir: None. S.W. Flavell: None. P. Sengupta: None. G. Haspel: None. M.B. Goodman: None. E.S. Boyden: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.03/III15

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 2017-18 B*CURED & NREF Research Fellowship Grant

NIH 1R01NS102727

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John Doerr

The HHMI-Simons Faculty Scholars Program

Open Philanthropy Project

NIH 1R01MH110932

Title: Multiplexed expansion microscopy in clinical specimens of normal brain and gliomas

Authors: *P. VALDES¹, Y. ZHAO², C. C. TORRES³, E. COSTA⁴, K. SHAH⁵, E. A. CHIOCCA⁵, E. S. BOYDEN³

¹Harvard Med. School/Brigham and Women's Hospital, Boston, MA; ²Carnegie Mellon, Pittsburgh, PA; ³MIT, Cambridge, MA; ⁴Brain and Cognitive Sci., MIT, Brooklyn, NY; ⁵Dept. Neurosurg., Brigham and Women's Hospital/Harvard Med. Sch., Boston, MA

Abstract: Imaging of normal and pathological states of the brain requires the ability to analyze multiplexed molecular information, with nanoscale precision, across extended 3-D tissues. Here we present multiplexed expansion microscopy, a new technology that enables super-resolution imaging of an arbitrary number of simultaneous molecular targets to aid in the discovery of new

mechanisms of human brain function as well as of pathological states such as brain tumors. Formalin-fixed paraffin-embedded clinical samples of normal human brain and human glioblastoma (GBM) tissue were immunostained, and pre-expansion images acquired with a super-resolution structured illumination microscope for later comparison. Tissues were then chemically modified with Acryloyl-X followed by hydrogel polymer embedding, then mechanically softened under denaturing, non-enzymatic conditions to retain epitopes, expanded ~4x in linear dimension with deionized water, and imaged with a conventional confocal microscope. Pre- and post-expansion images were compared for distortion analysis. Validation experiments demonstrated excellent isotropic expansion with spatial errors of ~5%. Post-expansion multiplexing was then optimized, resulting in gel embedding, and multi-round immunostaining and antibody stripping procedures. Antibody stripping yielded baseline fluorescence, ready for subsequent immunostaining rounds. In normal human hippocampus simultaneous imaging of over twelve targets revealed the dense astrocytic foot processes at the blood-brain barrier. In human GBM, imaging of the perivascular niche with eight different simultaneous targets, demonstrated the intricate network and interactions between proliferating tumor cells, astrocytic endfeet, vasculature components and the surrounding tumor microenvironment. This technology has the potential for broad application and dissemination given its ease of use, low cost, and biological relevance in performing highly multiplexed and nanoscale level imaging to help discover fundamental mechanisms in normal and disease states.

Disclosures: P. Valdes: None. Y. Zhao: None. C.C. Torres: None. E. Costa: None. K. Shah: None. E.A. Chiocca: None. E.S. Boyden: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.04/III16

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HHMI-Simons Faculty Scholars Program
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NIH 1R01MH110932
IARPA D16PC00008

Title: Multiplexed, targeted *in situ* sequencing of RNA in intact brain processed with expansion microscopy

Authors: *A. SINHA¹, A. T. WASSIE¹, S. ALON², D. GOODWIN¹, A. H. MARBLESTONE³, F. CHEN¹, G. M. CHURCH⁴, E. S. BOYDEN¹
²Media Lab., ¹MIT, Cambridge, MA; ³MIT Media Lab., Cambridge, MA; ⁴Harvard Med. Sch., Boston, MA

Abstract: The cellular content and subcellular localizations of RNAs within brain cells define cell types and states, and prescribe the mechanisms at hand for both high speed neural computations as well as long-term synaptic changes and disease progressions. While single-cell RNA sequencing has revealed a great diversity of cell types within the mammalian brain, such data discard the spatial context of cells as well as the distribution of RNAs throughout complex neuronal arbors. Recent developments in multiplexed RNA-FISH (seqFISH, MERFISH) and in-situ sequencing [1] have enabled the mapping of RNA across tissues and cells. However, many of these methods are limited by resolution because (1) such diffraction-limited methods lack the resolution to localize transcripts in nanoscale neuronal compartments such as synapses and processes and (2) the high density of mRNA in cells ($\sim 10^5$ /cell) makes it challenging to spatially resolve and map RNA species with high yield and precision.

Here, we present a strategy for highly multiplexed nanoscale imaging of RNA within the mouse brain using expansion microscopy (ExM) to decrowd RNA species for later targeted in situ sequencing. We use a small-molecule linker to covalently anchor RNA to a swellable polyelectrolyte gel synthesized densely and evenly throughout a biological specimen [2, 3]. After subsequent expansion, the RNA molecules are isotopically separated from one another, creating space for subsequent chemical and enzymatic steps to be performed with high yield. In the post-expanded state, oligonucleotide barcodes are hybridized to specific RNA transcripts of interest. The barcode sequences are subsequently amplified to produce a DNA library that is read out using in situ sequencing [4]. This process thus enables efficient super-resolution imaging of RNA identity, with diffraction-limited microscopes, throughout thick brain tissue sections. We demonstrate the utility of our technology by examining the synaptic localization of 35 different RNA species of interest within slices of mouse hippocampus.

[1] Nat Methods. 2013 Sep;10(9):857-60.

[2] Science. 2015 Jan 30;347(6221):543-8.

[3] Nat Methods. 2016 Aug;13(8):679-84.

[4] Science. 2014 Mar 21;343(6177):1360-3

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Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

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Program #/Poster #: 088.05/III17

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John Doerr

The HHMI-Simons Faculty Scholars Program

Open Philanthropy Project

NIH 1R01MH110932

IARPA D16PC00008

Title: Extracellular space labeling for connectomic analysis in mouse brain using expansion microscopy

Authors: *A. EMENARI¹, E. D. KARAGIANNIS², J. KANG², E. S. BOYDEN²

¹Cambridge, MA; ²MIT, Cambridge, MA

Abstract: To reconstruct connectomes, very large numbers of neurons, and the connections between them, must be resolved, with few errors. A common approach is to stain lipids in order to identify cellular membranes that delineate neural boundaries, followed by electron microscopy (1,2). To complement this approach, and extend the accessibility of connectomic strategies to light microscopy, we are working to develop ways of fluorescently labeling the extracellular space, resulting in negative contrast images of neurons in the light microscope. Used in conjunction with classical (e.g., lipid-bound) stains, extracellular space filling with fluorescent dyes may play a synergistic role, helping disambiguate cells at sites where the membrane label is inconsistent or broken. Our recent development of expansion microscopy (3) enables simple nanoscale resolution imaging of extended neural circuits, in the light microscope, and is finding widespread use in many parts of neuroscience. We are developing chemical strategies for filling the extracellular space with tags that, in conjunction with iterative expansion microscopy (ExM) (4), can enable the visualization of neural circuits in the mouse nervous system. In iExM, a sample of brain tissue is embedded in a dense swellable polymer, and then expanded, followed by a second round of polymer formation and expansion, resulting in 20x linear expansion before imaging, and effectively improving the final image resolution to 10 to 20 nm per pixel. We will discuss, in this poster, the chemical tags we are screening through, and show images of mouse neural circuits thus labeled and processed for iExM, evaluating the quality of the resultant neural morphology analysis.

1. Briggman, Kevin L., and David D. Bock. "Volume electron microscopy for neuronal circuit reconstruction." *Current opinion in neurobiology* 22.1 (2012): 154-161.
2. Denk, Winfried, and Heinz Horstmann. "Serial block-face scanning electron microscopy to reconstruct three-dimensional tissue nanostructure." *PLoS biology* 2.11 (2004): e329.
3. Chen, Fei, Paul W. Tillberg, and Edward S. Boyden. "Expansion microscopy." *Science* (2015): 1260088.
4. Chang, Jae-Byum, et al. "Iterative expansion microscopy." *Nature methods* 14.6 (2017): 593

Disclosures: A. Emenari: None. E.D. Karagiannis: None. J. Kang: None. E.S. Boyden: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.06/III18

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

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John Doerr

the HHMI-Simons Faculty Scholars Program

Open Philanthropy Project

NIH 1R01MH110932

IARPA D16PC00008

Title: Extracellular space labeling of the zebrafish brain using expansion microscopy

Authors: ***J. KANG**^{1,5}, E. HOSSEINI², E. D. KARAGIANNIS¹, A. EMENARI², T. SHIN³, C.-C. YU¹, E. JUNG¹, K. D. PIATKEVICH⁴, E. S. BOYDEN¹

²Brain and Cognitive Sci., ³Media Lab. - Synthetic NeuroBiology, ⁴Media Lab., ¹MIT, Cambridge, MA; ⁵John A. Paulson Sch. of Engin. and Applied Sci., Harvard Univ., Cambridge, MA

Abstract: J-SK and EH contributed to this work equally.

The morphology of neurons in brain circuits has classically been reconstructed from lipid stains or intracellular filling (e.g., via biocytin fills or brainbow expression). However, in principle, neurons could be reconstructed by imaging the surrounding extracellular space, given a suitable contrast agent. In such a case, the labeling of the extracellular space could be synergistic with, and facilitate the analysis of, cellular labeling with a small molecule or genetically encoded lipid or cytoplasmic marker. That is, the labeled extracellular space could help with error correction of the tracing of the lipid or cytoplasmic stain. As a method of nanoscale resolution imaging of intact brain circuits, we utilize our recently invented technique of expansion microscopy (ExM; *Science* (2015) 347(6221):543-548), which permits 3-D imaging of intact neural circuits with up to 10-20 nm precision in its most recently published form (*Nature Methods* (2017) 14:593-599). In short, ExM enables few-nanometer resolution imaging through the physical magnification of biological specimens, followed by imaging on conventional, high-speed, diffraction-limited optics. In our current project, we have been screening through libraries of chemicals, including small molecules as well as proteins, to determine which ones optimally enable the labeling of the extracellular space in the brain of the larval zebrafish, an important model organism for which we recently developed expansion microscopy protocols (*Proceedings of the National Academy of Sciences* (2017) 114(50):E10799-E10808). By identifying dense labels of the extracellular

space that are compatible with larval zebrafish brains, and chemically compatible with ExM, we aim to enable connectomics of entire vertebrate brains to become a routine and feasible technique for deployment into everyday neuroscience.

Disclosures: **J. Kang:** None. **E. Hosseini:** None. **E.D. Karagiannis:** None. **A. Emenari:** None. **T. Shin:** None. **C. Yu:** None. **E. Jung:** None. **K.D. Piatkevich:** None. **E.S. Boyden:** None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.07/III19

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

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John Doerr
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Open Philanthropy Project
NIH 1R01MH110932
IARPA D16PC00008

Title: *In situ* mapping of RNA at subcellular resolution using expansion sequencing (ExSeq) in intact brain tissue

Authors: ***D. GOODWIN**¹, S. ALON¹, F. CHEN¹, A. WASSIE¹, A. PAYNE¹, A. SINHA¹, H.-J. SUK¹, E. DAUGHARTHY², P. REGINATO¹, N. PAK¹, Y. BANDO³, K. MARRETT⁴, A. KAJITA⁴, R. WANG¹, P. W. TILLBERG⁵, A. MARBLESTONE¹, G. CHURCH⁶, E. S. BOYDEN¹

¹MIT, Cambridge, MA; ²ReadCoor, Cambridge, MA; ³Toshiba Memory America, Inc., San Jose, CA; ⁴Fixstars Solutions, Inc, Cambridge, MA; ⁵Janelia Res. Campus, Ashburn, VA; ⁶Harvard Med. Sch., Boston, MA

Abstract: Mapping the spatial distribution of transcripts throughout the complex morphologies of neurons in intact neural circuitry is important for understanding synaptic plasticity, learning and memory, and cell types and states in normal and pathological conditions [1]. We have developed expansion sequencing (ExSeq), which utilizes expansion microscopy (ExM) [2] to anchor proteins [3] and nucleic acids [4] of a specimen to an in situ-synthesized highly swellable hydrogel, followed by sequencing individual transcripts using fluorescent in situ sequencing (FISSEQ) [5]. We have focused, over the last year, on making the sequencing and computational protocols portable and efficient for practical use. First, we addressed the issue of in situ

sequencing data producing short reads (5-30 bases), which are difficult to align against the genome. We have developed a method to augment in situ sequencing with ex situ Illumina sequencing. In short, we extract amplified cDNA from the expanded sample after in situ sequencing, and then use conventional Illumina chemistry to fully sequence these extracted cDNAs. By augmenting the in-situ reads by ex situ information, we can associate long read sequences, up to 300 bases long, with each point in the tissue. Second, we addressed the issue of computational extraction of the in situ sequence reads from 3D imaging data. We have built a robust pipeline for registering each image volume from a microscope into a common coordinate space, during the 15-30 rounds of chemistry and imaging required for in situ sequencing. The optimized registration pipeline significantly increases the base calling accuracy of ExSeq. Leveraging the above improvements, we have generated tens of thousands of nanoscale-localized sequencing reads with an average length of ~100 bases from hundreds of neurons in a 50 micron thick slice of the mouse hippocampus. Using ExSeq, users can expand brain circuits and then sequence the RNAs within expanded tissue, resolving transcripts throughout neural circuits, and enabling systematic cell type and cell state classification in health and disease.

References:

- [1] J. Neuro 36(45):11418 –11426
- [2] Science 347:543-548
- [3] Nat Biotechnol. 2016 Sep;34(9):987-92
- [4] Nat Methods. 2016 Aug;13(8):679-84
- [5] Science 343:1360-1363

Disclosures: **D. Goodwin:** None. **S. Alon:** None. **F. Chen:** None. **A. Wassie:** None. **A. Payne:** None. **A. Sinha:** None. **H. Suk:** None. **E. Daugharthy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReadCoor Inc. **P. Reginato:** None. **N. Pak:** None. **Y. Bando:** None. **K. Marrett:** None. **A. Kajita:** None. **R. Wang:** None. **P.W. Tillberg:** None. **A. Marblestone:** None. **G. Church:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReadCoor Inc. **E.S. Boyden:** None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.08/III20

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1R01NS102727

NIH 1R01EB024261

John Doerr

the HHMI-Simons Faculty Scholars Program

Open Philanthropy Project
NIH 1R01MH110932
IARPA D16PC00008

Title: Iterative direct expansion microscopy

Authors: ***D. SARKAR**^{1,2}, A. T. WASSIE³, K. PIATKEVICH², T. TARR⁴, A. TANG⁴, T. BLANPIED⁴, E. BOYDEN^{2,3,1}

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Abstract: We recently discovered that it was possible to beat the diffraction limit through physical magnification of biological specimens, by embedding them in dense, swellable polyelectrolyte gels (Science (2015) 347(6221):543-548). The original process, which we called expansion microscopy (ExM), achieved a 4.5x linear expansion (i.e., a 300 nm diffraction limited lens would now have a resolution of $300 / 4.5 \approx 60$ nm). We also showed that, by iterating the polymerization and expansion process (iExM), we could achieve higher expansion factors ($4.5 \times 4.5 \sim 20x$, enabling a resolution of $300/20 \sim 15$ nm; Nature Methods (2017) 14, 593–599). However, the original form of iExM required us to discard the original biomolecules, replacing them with a polymer-anchored DNA oligo (targeted to a biomolecule of interest via an antibody administered pre-expansion) that could effect the transfer of information from the first gel to the second gel. However, this precludes multiplexed analysis via repeated staining, and also results in limited resolution due to the fact that the antibody must be administered first, and thus the size of the antibody becomes the key factor limiting resolution.

Here, we report a new form of iterative expansion microscopy which addresses both of these problems – enabling the preservation of biomolecules throughout the entire process, and also allowing for antibodies and other probes to be delivered at the end of the process, greatly improving resolution. Our new method, which we call iterated direct ExM (idExM), enables high expansion factors (20x to 100x) to be achieved, and may lead to resolution on the scale of individual biomolecules (<10 nm resolution). idExM overcomes the limit of all previous super-resolution techniques, where the effective resolution is limited by the size of the labels (eg. primary and secondary antibodies which are about 20-30 nm in total size). This may, in principle, result in resolutions of 1 nm or less. idExM also de-crowds biomolecules through iterative expansion, allowing access of antibodies to epitopes that may not otherwise be accessible for viewing by existing super-resolution methods. We are applying idExM to the visualization of detailed synaptic architectures in intact brain circuits.

Disclosures: **D. Sarkar:** None. **A.T. Wassie:** None. **K. Piatkevich:** None. **T. Tarr:** None. **A. Tang:** None. **T. Blanpied:** None. **E. Boyden:** None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.09/III21

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1R01NS102727

John Doerr

NSF Grant 1734870

the HHMI-Simons Faculty Scholars Program

Human Frontier Science Program RGP0015/2016

Open Philanthropy Project

NIH 1R43MH109332

Title: Robust, millivolt-resolution, high-speed neural voltage imaging in multiple species

Authors: *E. JUNG¹, K. PIATKEVICH¹, C. STRAUB², C. LINGHU¹, D. PARK¹, H.-J. SUK¹, D. HOCHBAUM², D. GOODWIN¹, E. PNEVMATIKAKIS³, N. PAK¹, T. KAWASHIMA⁴, C.-T. YANG⁴, J. RHOADES¹, O. SHEMESH¹, S. ASANO¹, Y. YOON¹, L. FREIFELD¹, J. SAULNIER², C. RIEGLER⁵, F. ENGERT⁵, T. E. HUGHES⁶, M. DROBIZHEV⁶, B. BALINT⁷, M. AHRENS⁴, S. FLAVELL¹, B. SABATINI², E. BOYDEN¹

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Abstract: An ideal genetically encoded fluorescent voltage indicator would localize well to the plasma membrane, be bright and exhibit high signal to noise ratio, exhibit large and linear fluorescent changes in response to voltage fluctuations, respond to changes in voltage rapidly enough to preserve the fidelity of spiking, exhibit stable (*i.e.*, non-photobleaching) fluorescence over timescales appropriate for conducting a biological experiment, present zero or minimal side effects, and be compatible with optogenetic control of neural activity. To develop a fluorescent voltage reporter useful in multiple neuroscience contexts, we developed a directed molecular evolution approach that enables multiple properties of a fluorescent voltage sensor to be simultaneously optimized. In particular, we adapted robotic cell picking for the isolation of single mammalian cells expressing individual members of a large library of fluorescent voltage sensor candidates, based upon three parameters -- brightness, localization, and voltage sensitivity. The result, the fluorescent voltage sensor Archon1 (Nat. Chem. Bio. 14, 352-360 (2018)), exhibits good performance along multiple dimensions of parameter desired in a fluorescent voltage reporter - good localization, high signal to noise ratio, large and linear

fluorescent changes, high speed of response, low photobleaching, and compatibility with optogenetic control. Archon1, therefore, represents a practical voltage reporter that may find widespread use in neuroscience. We demonstrated the utility of Archon1 in multiple species and in multiple research groups by imaging subthreshold (e.g., ~5 mV) synaptic activity in mouse cortical brain slices, high speed spiking and subthreshold activity in the larval zebrafish brain, and neural responses synaptically downstream of optogenetically controlled neurons in *C. elegans*. Thus, Archon1 not only represents the power of multidimensional protein engineering, but presents a practical tool for neural circuit deconstruction. We are continuing to evolve and optimize Archon1 with our directed evolution strategy, and also to create supporting tools (e.g., methodologies that link structure and function of nervous systems) so that such voltage imaging data can be interpreted in the context of cell types and connectomes.

Disclosures: **E. Jung:** None. **K. Piatkevich:** None. **C. Straub:** None. **C. Linghu:** None. **D. Park:** None. **H. Suk:** None. **D. Hochbaum:** None. **D. Goodwin:** None. **E. Pnevmatikakis:** None. **N. Pak:** None. **T. Kawashima:** None. **C. Yang:** None. **J. Rhoades:** None. **O. Shemesh:** None. **S. Asano:** None. **Y. Yoon:** None. **L. Freifeld:** None. **J. Saulnier:** None. **C. Riegler:** None. **F. Engert:** None. **T.E. Hughes:** None. **M. Drobizhev:** None. **B. Balint:** None. **M. Ahrens:** None. **S. Flavell:** None. **B. Sabatini:** None. **E. Boyden:** None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.10/DP13/III22

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Charles Hieken Ludwig Foundation

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John Doerr

NSF Grant 1734870

the HHMI-Simons Faculty Scholars Program

Human Frontier Science Program RGP0015/2016

Open Philanthropy Project

Title: Precision calcium imaging of dense neural populations via a cell body-targeted calcium indicator

Authors: ***O. A. SHEMESH**¹, **C. LINGHU**¹, **K. PIATKEVICH**¹, **D. GOODWIN**¹, **H. GRITTON**⁷, **R. GAO**², **M. F. ROMANO**⁷, **H.-A. TSENG**⁸, **S. BENSUSSEN**⁸, **S. NARAYAN**⁹, **C.-T. YANG**⁹, **L. FREIFELD**³, **C. SICILIANO**⁴, **I. GUPTA**¹, **N. PAK**¹, **Y.-G. YOON**⁴, **J. F. ULLMANN**¹⁰, **Z. R. SHEINKOPF**¹, **S. ASANO**⁴, **W.-M. PARK**⁵, **A. KEATING**⁵, **J. REIMER**¹¹, **K. M. TYE**⁶, **A. S. TOLIAS**¹¹, **X. HAN**⁷, **M. B. AHRENS**¹², **E. S. BOYDEN**⁴

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Abstract: Methods for one-photon fluorescent imaging of calcium dynamics in vivo are popular due to their ability to simultaneously capture the dynamics of hundreds of neurons across large fields of view, at a low equipment complexity and cost. In contrast to two-photon methods, however, one-photon methods suffer from higher levels of crosstalk between cell bodies and the surrounding neuropil, resulting in decreased signal-to-noise and artifactual correlations of neural activity. Here we address this problem by engineering cell body-targeted variants of the fluorescent calcium indicator GCaMP6f. We screened fusions of GCaMP6f to both natural as well as engineered peptides, and identified fusions that localized GCaMP6f to within approximately 50 microns of the cell body of neurons in live mice and larval zebrafish. One-photon imaging of soma-targeted GCaMP6f in dense neural circuits in larval zebrafish and in mice reported a decrease in artifactual spikes from neuropil, an increased signal-to-noise ratio, and decreased artifactual correlation across neurons. Thus, soma-targeting of GCaMP may facilitate even greater usage of simple, powerful, one-photon methods of population imaging of neural calcium dynamics.

Disclosures: **O.A. Shemesh:** None. **C. Linghu:** None. **K. Piatkevich:** None. **D. Goodwin:** None. **H. Gritton:** None. **R. Gao:** None. **M.F. Romano:** None. **H. Tseng:** None. **S. Bensussen:** None. **S. Narayan:** None. **C. Yang:** None. **L. Freifeld:** None. **C. Siciliano:** None. **I. Gupta:** None. **N. Pak:** None. **Y. Yoon:** None. **J.F. Ullmann:** None. **Z.R. Sheinkopf:** None. **S. Asano:** None. **W. Park:** None. **A. Keating:** None. **J. Reimer:** None. **K.M. Tye:** None. **A.S. Tolias:** None. **X. Han:** None. **M.B. Ahrens:** None. **E.S. Boyden:** None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.11/III23

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1R01NS102727

John Doerr

The HHMI-Simons Faculty Scholars Program

NIH R01 MH103910-05

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Broad Fellows Program
NIH 2R01DA029639

Title: Transcriptional RNA associated memory for molecular recording of neural activity

Authors: *S. G. RODRIQUES¹, L. M. CHEN⁵, S. LIU², E. D. ZHONG³, J. R. SCHERRER⁴, E. S. BOYDEN¹, F. CHEN⁵

²Hlth. Sci. and Technol., ³Computat. and Systems Biol., ⁴Physics, ¹MIT, Cambridge, MA;

⁵Broad Inst. of Harvard and MIT, Cambridge, MA

Abstract: The ability to encode the temporal activity of biological systems into nucleic acid sequences would open up new opportunities for non-invasive monitoring of neural, developmental, and environmental activity. Although several approaches have been taken towards the development of nucleic-acid based temporal recording systems, almost all systems demonstrated thus far operate exclusively in bacteria and have temporal resolutions on the order of days. Specifically, no system has yet been demonstrated in mammalian cells that is capable of recording the time since an event has occurred. Here, we demonstrate a new molecular recording system that allows us to infer the timing of specific transcriptional events that occur in mammalian cells, including neurons, using RNA sequencing up to 12 hours after the event occurred. In our system, RNA editing is used to record the time-course of transcriptional activity into the sequence of reporter RNA elements (repRNA). These repRNAs are produced in response to endogenous or exogenous cellular signals, such as a small molecule, light, transcription factor signaling, or neuronal activity. The repRNAs are then edited over a period of hours, allowing the age of a specific population of repRNAs (and hence the time of the transcriptional activity that produced them) to be inferred by the number of edits that have accumulated in that population. This method, which we refer to as T-RAM (Transcriptional RNA-Associated Memory), allows us to infer the timing of specific transcriptional events with 30 minute resolution. Different transcriptional events as well as cellular populations can be easily barcoded and multiplexed via nucleic acid barcodes. The system can be extended to detect transcriptional events in single cells and developmental signals. Thus, this system will allow for non-invasive recording of neural and developmental activity in an entire organism.

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Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.12/III24

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Charles Hieken
Ludwig Foundation
NIH 1R01NS102727
John Doerr
NSF Grant 1734870
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Human Frontier Science Program RGP0015/2016

Title: Sparse decomposition light-field microscopy for high speed 3-D imaging of neuronal activity

Authors: *Z. WANG^{1,9}, Y.-G. YOON^{1,2}, N. PAK^{1,3}, D. PARK¹, P. DAI^{1,4}, J. KANG^{1,10}, H.-J. SUK^{1,5}, K. WANG^{11,12,13,14}, E. S. BOYDEN^{1,4,6,7,8}

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Abstract: Light-field microscopy (LFM) can support imaging of the entire *C. elegans* nervous system and the entire larval zebrafish (*Danio rerio*) brain at high speeds (Nature Methods (2014) 11:727-730), but the spatial resolution obtained was insufficient to yield single-cell resolution imaging in many contexts, such as in behaving zebrafish larvae. More recently, eXtended field of view LFM (XLFM) (eLife (2017) 6:e28158), which simultaneously optimizes imaging volume and spatial resolution, and avoids square-shaped artifacts near the focal plane by placing the micro-lens array on the pupil plane of the system, was developed to offer better spatial resolution, but separating signals from nearby neurons is still a challenge. Here we introduce sparse decomposition light-field microscopy (SDLFM), a computational imaging technique that further improves the ability of XLFM, and that allows for the imaging of neuronal activity with very high spatiotemporal resolution. With this technique, the spatial resolution can be improved and hence neuronal activity can be accurately recovered, even from nearby neurons. We show the power of SDLFM by demonstrating *in vivo* imaging of neuronal activity of whole brains of larval zebrafish and adult fruit flies (*Drosophila melanogaster*) with high volume rates up to 50 Hz. (Yoon and Wang are co-first authors.)

Disclosures: Z. Wang: None. Y. Yoon: None. N. Pak: None. D. Park: None. P. Dai: None. J. Kang: None. H. Suk: None. K. Wang: None. E.S. Boyden: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.13/III25

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Charles Hieken

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John Doerr

NSF Grant 1734870

the HHMI-Simons Faculty Scholars Program

Open Philanthropy Project

Title: High speed voltage imaging and optogenetic control of neural activity in living mouse brain

Authors: *M. H. MURDOCK¹, K. D. PIATKEVICH¹, S. BENSUSSEN², H.-A. TSENG², D. GOODWIN¹, C. LINGHU¹, O. A. SHEMESH¹, S. SHROFF², E. JUNG¹, A. YANG¹, A. WASSIE¹, L.-H. TSAI¹, X. HAN², E. S. BOYDEN¹

¹MIT, Cambridge, MA; ²Biomed. Engin., Boston Univ., Boston, MA

Abstract: While single cell anatomical and physiological techniques have generated a great deal of insight into the mechanisms governing the operation of individual neurons, new technologies are needed to help us understand how individual neurons work together as networks to yield emergent functions such as cognition and behavior. Electrophysiological techniques are exquisitely sensitive and possess high temporal resolution, but have generally been restricted to making measurements on a small number of cells relative to those involved with a given neural computation. Calcium imaging has recently emerged as a way to analyze large neural populations, but lacks the temporal resolution to report on individual spikes and synaptic events, key to many important brain functions. Using directed molecular evolution and a robotic, microscopy-guided, multidimensional cell picking approach, we recently generated Archon1, a genetically encoded voltage indicator (Piatkevich et al, Nat Chem Bio 2018). Here, we discuss somArchon, a variant of Archon1 containing a soma-localization sequence that restricts voltage reporting to the cell soma, and greatly reduces fluorescence of the neuropil. We illustrate somArchon's ability to resolve subthreshold and synaptic neural activity in neurons, even through cranial windows of awake, behaving mice. We also report all optical electrophysiology in the living mouse brain using a bi-cistronic approach to co-express somArchon with specific channelrhodopsin variants. Following voltage imaging, we exploit expansion microscopy (ExM) and fluorescence in situ hybridization to molecularly define cell types of interest, enabling the

facile linkage between structure and function in the mouse brain. In summary, somArchon and ExM may be useful for population analysis of how specific cells and cell types contribute to complex brain functions, both normal and abnormal.

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Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.14/III26

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

Support: Lundbeckfonden
University of Copenhagen 2016 Program of Excellence

Title: Effects of sleep deprivation on theory of visual attention (TVA) parameters in the mouse 5-choice serial reaction time task

Authors: ***C. M. FITZPATRICK**, D. P. D. WOLDBYE, U. GETHER, J. T. ANDREASEN
Univ. of Copenhagen, Kobenhavn N, Denmark

Abstract: Total sleep deprivation (TSD) can deleteriously affect attentional processes in both humans and rodents; Understanding its specific effects on attention can improve discovery of nootropics. The 5-choice serial reaction time task (5-CSRTT) is a paradigm extensively used to assess attentional control in rodents. Many human attention studies have used testing based on Theory of Visual Attention (TVA) to estimate visual processing speeds and other attentional capacity parameters. We aimed to assess the effects of TSD on 5-CSRTT performance and then derive attentional parameters analogous to TVA-based measures. We assessed the effects of 12 h TSD in 18 male, baseline-trained C57BL/6J mice in a 5-CSRTT variable stimulus duration challenge (0.1, 0.2, 0.4, 0.7, 1.1, 1.8 s). Mice were kept awake based on continuous visual observation (0-6 h) and gentle handling (6-12 h). This study was counter-balanced and controlled, so that one half of animals experienced TSD on Day 1 and the other half on Day 2. TSD effects were also examined on animals separated into high- (HA) and low-attentive subgroups (both n=6). Percentage correct values were modelled using TVA to obtain estimates of visual processing speeds, perceptual thresholds and motor baselines. Paired t-tests (overall performance) and two-way repeated measures ANOVA (per stimulus duration) approaches were chosen to analyse data. TSD reduced overall response accuracy ($F_{1,17}=6.88$, $p<0.05$) when all data were compiled. No other 5-CSRTT or TVA parameters were affected when all animals were analysed together. In the HA subgroup, TSD demonstrated a near-significantly trend to reduce

overall percentage omitted ($F_{1,5}=5.44$, $p=0.067$) and correct trials ($F_{1,5}=6.32$, $p=0.0536$). When assessed per stimulus duration, there was a near-significant effect of TSD on percentage omissions ($F_{1,5}= 5.44$, $p=0.067$) in HA animals, with TSD increasing omitted trials at the 0.7 s ($p<0.01$) probe. Likewise, there was a near-significant effect of TSD on percentage correct responses ($F_{1,5}=6.29$, $p=0.0539$) in HA mice, with TSD reducing performance at the 0.1 ($p<0.01$) and 0.7 ($p<0.05$) s lengths. TSD also displayed trend-level reductions in TVA-based visual processing speed ($F_{1,5}=5.35$, $p=0.0686$) in these HA animals. No significant alterations in 5-CSRTT or TVA performance were observed in either the mid- or low-attentive subgroups. TSD induced subtle impairments in 5-CSRTT performance and visual processing speed, particularly in the HA subgroup. Additional experiments are required to increase the n value to increase the statistical robustness of this study and allow for future studies with putative nootropics.

Disclosures: D.P.D. Woldbye: None. U. Gether: None. J.T. Andreasen: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.15/III27

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

Title: PICK1 modulation of protein kinase A (PKA) activity

Authors: *M. B. LEVER¹, G. DI MOLFETTA², K. L. MADSEN²

¹Dept. of Neurosci., Univ. of Copenhagen, Copenhagen N, Denmark; ²Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Separate lines of evidence show the importance of PICK1 and PKA in synaptic plasticity and associated pathologies such as neuropathic pain, psychiatric disorder and Alzheimer's disease. We have found a novel non-canonical PDZ interaction of PICK1 and PKA and we present here characterization of the interaction that implies regulation of PKA activity by PICK1. In heterologous co-immunoprecipitation assays in HEK cells we show that the PICK1-PKA interaction is altered with Acrodysostosis-disease-causing-PKA-mutations, implying that the PICK1-PKA interaction is important in physiology. In co-immunoprecipitation assays from the hippocampus we find that cAMP binding to the PKA regulatory subunits reduces the interaction of PICK1 and PKA. Knockdown of PICK1 in PC12 cells, for example, results in a reduction in the peak fluorescence of the PKA FRET reporter AKAR, suggesting a reduction in the phosphorylation of PKA target residues when PICK1 is absent. Using a cAMP-induced PKA activity assay in fluorescence polarization we uncover the functional modulation of PKA by PICK1. We believe this insight will be relevant in many fundamental cellular contexts, but particularly in those relating to synaptic plasticity and related pathologies.

Disclosures: M.B. Lever: None. G. di Molfetta: None. K.L. Madsen: None.

Poster

088. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques I

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 088.16/III28

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

Support: The Lundbeck Foundation
The Danish Medical Research Council

Title: Knock-in mice expressing disease-associated dopamine transporter mutations: A novel model for ADHD?

Authors: *L. K. KONRAD, F. HERBOG, F. L. M. BERLIN, U. GETHER
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Abstract: Dysregulation of dopamine signalling in the brain has been associated with psychiatric disorders, such as ADHD, autism, schizophrenia, and with movement disorders such as Parkinson's disease. Missense mutations in the dopamine transporter (DAT) can lead to dysfunctional dopamine homeostasis and cause not only a cellular physiopathology but also noticeable phenotypes in mice and humans. Several rare coding variants have been discovered in the *SLC6A3* gene encoding DAT in ADHD patients and more in other patients with psychiatric disorders. We have identified a male patient who was compound heterozygous for hDAT^{I312F} and hDAT^{D421N} mutations and diagnosed with atypical Parkinsonism and ADHD. He suffered from intellectual impairment, learning difficulties, lack of impulse control, forming and upholding social relationships, and tremors progressing in severity and extensiveness. The two residues I312 and D421 in are highly conserved across species and part of the membrane-spanning domains of DAT. Both mutations have been characterised in-vitro and ex-vivo and show notable decrease of transport capacity. Here, we show results from an ongoing study focusing on the characterization of a mouse model carrying the corresponding mutations mDAT^{I311F} and mDAT^{D420N} found in the patient. The physical performance of compound heterozygous mice (cHET) and their wild type (WT) littermates has been examined using a battery of classical behavioural tasks, including movement tracking in the open field and in the elevated plus maze, evaluation of motor skills, such as motor coordination, motor learning, grasping and climbing skills at young adult age. The mice were further tested for abnormal clasping. Elucidation of the reaction to available drugs used in the treatment of ADHD symptoms is currently ongoing. Overall, the compound heterozygous mice are smaller than their littermates and display a remarkable novelty-driven hyperactivity and pronounced exploratory behaviour. Clasping as shown previously in various models for Parkinsonism could not be observed. Repetitive D-

amphetamine boli seem to counteract hyperactive and stressed behaviour. Altogether, the behavioural assessment indicates an ADHD-like phenotype.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 089.01/III29

Topic: I.06. Computation, Modeling, and Simulation

Support: EPSRC Grant EP/L0153/74/1

Title: Approximations for the firing rate dynamics of neurons modelled with dendrites and axon

Authors: *R. P. GOWERS¹, Y. TIMOFEEVA², M. J. RICHARDSON²

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Abstract: How different classes of neurons integrate stochastic synaptic input has been a subject of intense experimental and theoretical focus over the last 50 years. Many approaches have approximated the cell as electrotonically compact and focussed on the effect of intrinsic ion currents on the patterning of the outgoing spike train. Due partly to the sparsity of the experimental data required for model constraint, but also to the mathematical complexity involved, few analytical results are available for neurons with dendritic structure.

To examine how spatially distinct streams of stochastic synaptic drive are integrated in spatially extended neuron models, such as pyramidal cells, we have developed an upcrossing method that allows for an approximation of the steady-state firing rate and firing rate response. We present results from a variety of neuronal structures and demonstrate where spatially extended neurons have a qualitatively different response to point neuron models. Furthermore, this approach can be straightforwardly applied to quasi-active neuronal membranes to include the effects of the h-current that is present in the apical dendrites of pyramidal cells.

Disclosures: R.P. Gowers: None. Y. Timofeeva: None. M.J. Richardson: None.

Poster

089. Computation, Modeling, and Simulation: Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 089.02/III30

Topic: I.06. Computation, Modeling, and Simulation

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Title: Deep brain stimulation of afferent axon terminals

Authors: *K. L. BOWER, C. C. MCINTYRE
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Abstract: Background: Deep brain stimulation (DBS) of the subthalamic region is a proven treatment for late-stage Parkinson's disease. Recent experimental findings suggest that stimulation of "hyperdirect" subthalamic afferents arising from motor cortex likely play an important role in the therapeutic mechanisms of DBS. Therefore, the goal of this project was to quantify the response of terminating afferents (TA) to extracellular stimulation using a computational DBS model, and compare this response to the stimulation of fibers of passage. **Methods:** Multi-compartment cable models of structurally idealized branched terminating axons were created to imitate the structure of hyperdirect afferents in the subthalamic nucleus (STN). Four models were created with various degrees of branching complexity and axon diameters. Unbranched fibers of passage (FOP) were also created for comparison. A finite element model of the DBS electrode in a human head was used to solve the spatial voltage distribution from a DBS stimulus. Two different head models were analyzed to identify the robustness of termination effects: one simple model in which the head was considered as a single homogeneous, isotropic volume, and one realistic model including tissue heterogeneity and brain anisotropy. Consistent with reported anatomy of the hyperdirect pathway, axons were placed in the internal capsule of the head model, with collaterals projecting to the STN. Activation thresholds were determined by identifying the lowest stimulus amplitude that elicited an action potential which propagated to the ends of the axon. **Results:** Branching complexity of the terminating axonal arbor had little effect on the activation threshold. TAs generally exhibited lower thresholds than diameter-matched FOPs; however, some large diameter fibers showed the opposite trend at small axon-electrode distances. These results suggest that small diameter terminating axons are hyperexcitable compared to diameter-matched fibers of passage. Use of a realistic head model reduced activation thresholds of both FOPs and TAs, suggesting that brain anisotropy and tissue inhomogeneity are important components of DBS models. However, axonal recruitment order was unaffected by the head model, suggesting that general effects of axon terminations on DBS thresholds are consistent across simple and realistic head models. **Conclusions:** Hyperdirect axon collaterals in the STN, which have small diameters and terminate near the DBS electrode, may be hyperexcitable compared to equidistant, diameter-matched fibers of passage. As such, hyperdirect axons may be some of the lowest threshold neural elements recruited in STN DBS.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

Location: SDCC Halls B-H

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Title: Interplay of activation kinetics and derivative conductance determines resonance properties in a neuron model with I_h current

Authors: *R. D. PENA¹, C. C. CEBALLOS³, V. LIMA², A. C. ROQUE⁴

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Abstract: Neurons can display enhanced oscillatory response to periodic input signals of given frequencies, a phenomenon known as subthreshold resonance. The amplification of the neuron's response at preferred frequencies depends on the types and characteristics of ionic channels present in the neuronal membrane, such as the h-channel associated to the resonant hyperpolarization-activated current I_h . The specific modulation of the neuron's response under influence of I_h is still under debate. To tackle this problem, we used a Hodgkin-Huxley type neuron model with only leak and I_h currents. We derived equations that relate the biophysical features of I_h to the resonance frequency. The equations were verified through computational simulations in which the neuron model was submitted to the so-called "ZAP" function, which is an oscillatory input current with frequency that linearly increases in time. This function is commonly used in experimental protocols to study resonance in neurons and allows the determination of the frequency-dependent impedance magnitude profile of the neuron. Our results show that there are two main factors that determine existence and frequency of resonance in the neuron model: (i) the activation time constant of the I_h current; (ii) the derivative conductance which is the conductance to voltage derivative ratio (dg/dV) obtained by differentiating its current equation with respect to the voltage (dI_h/dV). The increment of both (i) and (ii) contributes to the appearance of resonance. In addition, we demonstrate that resonance is

voltage dependent due to (ii). Our results can be used to predict and explain resonance in neurons with the I_h current.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

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Topic: I.06. Computation, Modeling, and Simulation

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Title: A general method to generate artificial spike train populations

Authors: S. ABBASI¹, S. MARAN², *D. JAEGER²

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Abstract: Synaptic decoding of neural population activity at the single cell level presents a challenging question. One method to address this question in a rigorous way is to use detailed single neuron simulations with well-defined input patterns to study the input-output function of biophysically realistic neurons. In previous work we developed a method to create artificial spike trains (ASTs) that can match spike train properties of cerebellar Purkinje cells in order to study the cerebellar cortical-nuclear signal transformation. Here we generalize this method to create well defined artificial spike trains (ASTs) made from templates of different types of recorded neurons and further test the method with surrogate data.

The basic idea of our method is to use recorded neurons to construct rate templates of their activity using gaussians. Then we can draw gamma distributed spike trains from these rate templates to obtain ASTs with different regularity properties. We can scale templates to different firing rates, add a refractory period to the gamma distributions, and add well defined rate-correlations between multiple ASTs by manipulating the rate template. Here we first tested our method with constant rate templates, sinusoidal rate templates, and zap rate templates. We find that slow rate fluctuations (~1Hz) can be well captured by individual ASTs, but that faster rate fluctuations require a population average of ASTs to recapture the rate template. The ability to capture faster rate fluctuations is a function of the regularity (kappa parameter of the gamma distribution) and the rate of the ASTs that are being generated. These properties parameterize fundamental limits of coding rate fluctuations with noisy spike trains. The method was then applied to simulate spike trains from cortical pyramidal cell and cerebellar mossy fiber recordings. The results show good matches to the statistical properties and rate fluctuations of

the original spike trains. Using this method one can then create populations of realistic ASTs with controlled rate covariances and behavioral rate modulations as inputs to biophysically realistic neural simulations.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

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Program #/Poster #: 089.05/III33

Topic: I.06. Computation, Modeling, and Simulation

Title: Computational modeling of intrinsic cardiac neuron in a porcine model: Implication of the role of ion channels in generating action potential

Authors: *S. SALAVATIAN, M. LANKARANY¹, J. TOMPKINS², A. VINET³, G. KEMBER⁴, A. ARMOUR², M. VASEGHI², J. ARDELL²

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Abstract: The autonomic nervous system controls every aspect of cardiac function. Intrinsic cardiac nervous system (ICNS) acts as the final coordinator of regional cardiac indices which regulates the function of heart on a beat by beat basis. The underlying mechanism of the ICNS and how these neurons regulate the functionality of the heart is not fully understood. To better understand the behaviour of these neurons, we aimed to develop a single cardiac neuron model to investigate the response of these neurons to different stimuli. In an earlier study, a computational model of a cardiac neuron was developed in crustacean. However, the ICNS of crustacean is very different than the human. In our earlier investigation, we have found that intrinsic cardiac neurons in small species show different behaviour to the same stimulus than cardiac neurons in large mammalian. This is also due to the fact that some ion channels that contribute to the action potential in these species are different from large mammalian cardiac neurons. The main aim of the present work is to implement a computational model of an intrinsic cardiac model from a porcine heart which is very similar to human heart. In this study the heart was harvested from 4 Yorkshire pigs. Intrinsic cardiac neurons were collected from a ganglion in the inferior vena cava regions. Colored noise current was injected in the cell body as a random stimulus and ex-vivo intracellular recordings were obtained from 2 cells on each harvested cardiac ganglion. Total of 20 recordings were obtained using intracellular microelectrodes. In our Hodgkin-Huxley based computational model, we have modelled the following currents: fast and slow sodium I_{Na} , early outward I_A , a delayed outward I_{Kd} , and a calcium-dependent I_{KCa} potassium, persistent I_{CAS} and

transient I_{CAT} calcium, fast nicotinic synaptic I_{syn} , muscarinic I_{M} and the leak current from the recording electrode. Same colored noise stimulus was given to the model to fine tune the parameters and the intracellular recording from 5 recordings were used to train the model to generate similar shape action potential with the same timing. After training the model, 15 recordings were used to test and validate the computational model of the porcine intrinsic cardiac neuron. This model gives us a very important insight about the potential way of modulating these cardiac neurons by affecting an specific ion channels in a diseases states. We are currently doing ex-vivo intracellular recording from cardiac neurons in a heart attack porcine model to compare the single cardiac neuron model in normal vs myocardial infarction states.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 089.06/III34

Topic: B.10. Epilepsy

Title: Generating all-active biophysical models for human and mouse neurons

Authors: ***A. NANDI**¹, **A. BUCHIN**¹, **C. ANASTASSIOU**^{1,2}

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Abstract: The presence of voltage-dependent conductances along the dendritic morphology of single-neurons plays important roles to the information processing capabilities of cortical neurons [Koch, 1997]. Thus developing representative biophysical all-active models constrained by the electrophysiological data and morphological reconstructions, is one of the critical first step to probe into the computations of neural circuits. Although there have been significant contributions towards modeling single neurons [Hay et al, 2011, Gouwens et al, 2018], there is a broad scope to establish a systematic model generation workflow that estimates the active conductance parameters over all sections (soma, axon, apical and basal dendrite) in a neuron. At Allen Institute for Brain Science, as part of our large effort to understand cortical computations related to rodent visual pathways and network dynamics at pathological human brain states, we have created a large database consisting of slice physiology and morphology reconstructions from both mouse and human brain. Leveraging open source optimization tool BluePyOpt [Van Geit et al, 2016] based upon multi-objective evolutionary algorithms [Fortin et al, 2012] and state of the art high-performing computational resources, we developed a refined optimization pipeline to fit all-active models. This approach first prioritizes passive somatic features such as voltage deflection, decay time constant in response to a step current, then more nuanced subthreshold features e.g., sag in membrane potential during hyperpolarization and eventually

spiking characteristics of the voltage traces. We also introduce a cell specific final step to this optimization strategy where the corresponding model objective is modified to penalize features for which the model consistently underperforms. At this final stage to preserve the overall goodness-of-fit we allow perturbations only to certain parameters informed from sensitivity analysis [Tennøe et al, 2018] on the model for the specific features. We show that this approach results in all-active single-neuron models that better capture experimentally measured electrophysiology features compared to an unbiased approach. This layered strategy also facilitates a computationally efficient search of the parameter space by consistently improving the initial guess for the parameters at each step of the optimization.

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Poster

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Program #/Poster #: 089.07/III35

Topic: B.10. Epilepsy

Title: Comparison between model and experiments: Features of the extracellular spike waveform vary with different cell types

Authors: *Y. WEI, X. JIA, A. NANDI, K. DAI, S. OLSEN, C. A. ANASTASSIOU
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Abstract: The Allen Institute for Brain Science has a mission to understand cortical computations related to the rodent visual pathway. Part of this approach is to understand where do brain signals such as extracellular voltage recordings originate. In this study, we are interested how the activity of spikes, especially from different cell types, contributes to extracellular voltage recordings.

Here we combine computational modeling of extracellular recordings using biophysically realistic and fully reconstructed single-neuron representations of various cell types (incl. various classes of interneurons and pyramidal neurons) for both perisomatic (compartmental models with passive dendrites) and all-active (compartmental models with active dendrites) models in the rodent cortex together with *in vivo* extracellular recordings of single units from behaving rodent experiments. Based on recording from a new high-density extracellular probe, the Neuropixels [Jun et al, Nature, 2017], i.e. a silicon probe with densely packed recording sites in multiple columns along a thin linear shank that can be targeted to regions throughout the brain, offers the ability to measure extracellular action potential (EAP) signatures from multiple (up to 10) contacts *in vivo*. Based on their extracellular spike waveforms, the visual cortical neurons are classified into: fast spiking (FS) and regular spiking (RS) neurons. For different cell types of experimental and model data, we extract the extracellular features, such as the amplitude and the

width of the EAP, the peak latency, and the onset latency, from multi-channel recordings in freely moving animals. We find that the model shares similar features with the *in vivo* recordings: 1) the amplitude of the EAP reduces as the distance from electrodes and soma increases; 2) the amplitude and width have no significant correlation in the FS neurons, yet are significantly anti-correlated in most of RS neurons; 3) RS neurons often show back-propagating action potentials along apical dendrites in the all-active model similar as the experiments. By comparison these EAP-waveform features in simulations with experiments, we can understand how the morphology and active properties of dendrites of the neurons contribute to the extracellular recordings.

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Poster

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Title: Features of the extracellular action potential vary with the cardiac cycle: Toward *in vivo* classification of cells in the human and macaque brain

Authors: *C. P. MOSHER¹, Y. WEI², J. KAMINSKI¹, M. E. YOUNG³, P. H. RUDEBECK³, A. MAMELAK¹, C. ANASTASSIOU^{2,4}, U. RUTISHAUSER^{1,5}

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Abstract: Complex behaviors involve the recruitment and cooperation of various excitatory and inhibitory cell types within and across brain circuits. In rodents, the identification of putative excitatory cells and inhibitory basket cells has been achieved using features of spike waveforms from polytrode recordings. More recently, genetic markers and fluorescence imaging have been used to monitor inhibitory and excitatory cells *in vivo*. This level of detail is lacking for the human brain because detailed laminar depth recordings are rare and genetic manipulation *in vivo* isn't currently feasible, limiting our understanding of how different cell types give rise to

behavior.

Here we combine computational modeling of the extracellular field using biophysically realistic and fully reconstructed single-neuron representations of various cell types in rodent and human cortex together with *in vivo* recordings from humans and macaques to identify features of the extracellular action potential (EAP) that can be used for cell classification. Beyond conventional analysis of EAP-width and amplitude to identify cell class, we also analyze how EAP-features change with periodic motion caused by the heartbeat. Typically perceived as an unwanted effect that compromises data collection, we propose a surprising new hypothesis: the presence of temporally periodic motion artifacts such as cardioballistic motion allows the EAP to be sampled at multiple locations around a cell improving classification of cell types during behavior. By comparing experimental data to simulations of cells with known identity, we propose that different variations in EAP-features during motion relate to different cell types, offering a powerful new method for the identification of cell types *in vivo*.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

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Program #/Poster #: 089.09/III37

Topic: I.06. Computation, Modeling, and Simulation

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Title: Methods for fitting compartmental models to neuronal data

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Abstract: Compartmental modeling of neurons allows one to quickly and efficiently test how ion channels, distributed across neuronal compartments, contribute to activity. The quality of predictions generated from such models depends critically on the biophysical accuracy of the model. This accuracy can be improved through optimization, which constrains model parameters to best fit an empirical dataset. Depending on how optimization is implemented—both mathematically and experimentally—one can arrive at several solutions that all reasonably fit empirical datasets. Intuitively, as one increases the size and complexity of the target dataset, the number of models that accurately capture dataset properties decreases, theoretically leading to

one unique solution that satisfies all aspects of the dataset. Identifying such a solution is a challenge.

Here we present detailed analytical approach to guide model optimization towards a unique set of parameter values that best represent experimental data. As a test bed, we began with Mainen and Sjenowski's 1996 model of a cortical pyramidal cell, which has 12 free parameters describing ion channel distribution within different compartments. Initially we used the original values of the free parameters (named the target parameters) to create a dataset of voltage responses that represents the ground truth target data. Given this target dataset, our goal was to determine whether we could use optimization to arrive at similar parameter values when these values were unknown. We tested over 150 different stimulation protocols and 15 score functions, which compares the simulated data to the ground truth dataset, to determine which combination stimulation and score functions creates datasets that reliably constrain the model. Then we checked how sensitive each parameter was to different score functions. We found that 5 of the 12 parameters were sensitive to many different score functions. While these 5 could be constrained, the other 7 parameters were sensitive only to a small set of score functions. We therefore divided the remaining optimization process to several steps, iteratively constraining a subset of the parameters that were sensitive to the same stimulation protocols and score functions. With this approach, were able to constrain the parameters of the model and recover the original values. This suggests that iterative, sensitivity analysis-based optimization could allow for more accurate fitting of model parameters to empirical data. We are currently testing whether similar results can be obtained in more recently developed models, and whether similar approaches can be applied to data derived from neurons.

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Poster

089. Computation, Modeling, and Simulation: Cellular Models

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Topic: I.06. Computation, Modeling, and Simulation

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Title: Modeling repertoire of activity patterns for *Drosophila* multimodal sensory neurons

Authors: ***N. MAKSYMCHUK**, D. N. COX, G. S. CYMBALYUK
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Abstract: Spatio-temporal coding strategies that neurons use to distinguish between distinct stimuli remains an open question. Studying modality-specific neural activity patterns of *Drosophila* class III (CIII) multimodal sensory neurons has the potential to provide insights into this fundamental question. CIII neurons are activated by noxious cold and innocuous mechanical stimuli. These two distinct modalities, acute cold and gentle touch, elicit different types of behavior – full body contraction (CT) and head withdrawal, respectively. We hypothesize that each of these modalities is associated with a unique pattern of neuronal activity. CIII multimodality is mediated by the TRP channels Pkd2, Trpm, and NompC. We developed a computational model of CIII neurons that currently exhibits a wide spectrum of qualitatively different activity regimes. Depending on the choice of the parameter set, the model could show two different types of resting states: hyperpolarized or depolarized; fast bursting activity, and two types of spiking activity: small or large amplitude. The model exhibits bistability of large amplitude spiking and hyperpolarized rest state in some parameter ranges. These regimes are associated with different levels of $[Ca^{2+}]_i$: both resting states and small amplitude spiking produce low levels of $[Ca^{2+}]_i$, while large amplitude spiking and bursting produce high levels of $[Ca^{2+}]_i$. Inclusion of the I_{Trpm} , and I_{Pkd2} , allows us to consider the problem of coding modality-specific activity patterns by coordinated modality-specific activation of these two TRP currents. The basic model with I_{Pkd2} could represent an alternative scheme of the temperature coding following the sequence of transitions between regimes: small amplitude spiking, period doubling cascade, bursting, large amplitude spiking, co-existence of large amplitude spiking and rest state, rest state, co-existence of large amplitude spiking and rest state along with the temperature going down. This repertoire of regimes is common for biophysical models of neuronal activity equipped with slow and fast variables governing ionic currents. Finally, TRP channels are not only required for CIII-mediated behavior responses to noxious cold, but together with calcium-activated K^+ channels they finely tune optimal $[Ca^{2+}]_i$ levels and regulate neural activity patterns for coding modality specific CT behavior.

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Poster

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Program #/Poster #: 089.11/III39

Topic: I.06. Computation, Modeling, and Simulation

Title: Prosthetic brain repair possibilities using self assembly: A speculative approach and possible road map

Authors: *A. C. PARKER¹, K. YUE², R. LEE²

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Abstract: Convergence of unrelated disciplines often leads to innovation. Nanoparticles used for medical treatments, DNA self-assembly, magnetic stimulation of the brain, and knowledge of brain self-repair and plasticity are converging fields that could one day lead to neural prosthetics that repair local brain damage and damaged spinal neurons, restoring movement capabilities and even access to lost memories. Growth and shrinking of DNA microtubules under external control has been demonstrated by Green, Franco et al. in the laboratory, brain stimulation using magnetic fields has been demonstrated (e.g. Polania et al. and Rossini et al.), the use of carbon nanotubes to mimic synapses has been shown in the laboratory by Joshi, Parker et al., and using carbon nanotubes to mimic neurons at UCLA, growing and using nanowires to encourage and guide retinal growth has been recently shown Piret et al., electronic neuromorphic circuits using astrocytes for synapse and neural repair have been simulated by Lee and Parker, and treatment with magnetic nanoparticles has been proposed by Yue et al. In parallel with these breakthroughs, hippocampal prosthetics that restore memory have been demonstrated (Hampson, Song, Deadwyler, Berger et al.). These preliminary techniques, when mature and integrated into a working system, could lead to nanoassembly in the brain of artificial axons, synapses or astrocytes that connect active areas of the brain, remapping neural signals that have been lost due to local damage (e.g. injury or stroke). Injection of nanoparticles into brain regions, followed by application of directional magnetic fields, could assemble axons and possibly simplified synapses that bridge between damaged areas or could build artificial astrocytes that encourage and guide their development. The technologies required for this bold approach are in their infancy. This abstract is designed to stimulate discussion and innovation leading to such a brain prosthesis some decades in the future. The manner in which the neural prosthetic could work to repair local damage is as follows: Injection of nanoparticles, either locally or intravenously, could be followed by application of focused magnetic fields that assembled the nanoparticles into artificial glial cells that encourage and scaffold viable neurons or into tubules or wires that connected active neurons in the region of damage. More sophisticated assembly could result in nanosynapses and spiking circuits that mimicked neurons in the distant future. Such connections could also be encouraged by stimulating nearby viable astrocytes with nanoparticles designed to invoke calcium waves that encourage neural connections.

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Poster

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HSF: CAPES

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Title: Computational model of an alpha motor neuron to study the progression of amyotrophic lateral sclerosis

Authors: *D. E. COSTA MATOSO¹, H. SANCHEZ FERNANDES², L. A. ELIAS³
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Abstract: Recent studies employed computational models of motor neurons (MNs) to evaluate the biophysical mechanisms behind the neurodegeneration observed in genetically modified animal models of ALS. These models represented the morphology, electrophysiology, and bioenergetics of MNs in different stages of ALS. Nonetheless, to the best of our knowledge, no previous computational study systematically investigated the biophysical changes observed during the progression of ALS. Here, the aim was to parameterize a computationally efficient model of an alpha MN to represent two conditions in the early stage of ALS, namely the hyperexcitability observed in embryos and the normal excitability due to compensatory mechanisms observed in neonatal cells. We represented an FF-type MN using a two-compartment mathematical model. The following voltage-gated ion channels were included in the soma: Na⁺, persistent Na⁺, fast K⁺, and slow K⁺. An L-type Ca⁺⁺ channel was included in the dendrite. Morphological and electrophysiological parameters were initially set so that the model could reproduce data from cat MNs. Changes in dendrite morphology, Na⁺ and Ca⁺⁺ persistent inward currents (PICs), and slow K⁺ current were performed to evaluate their influence on electrophysiological properties of the model. Input resistance, action potential amplitude, AHP amplitude and duration, rheobase, and the gain of the f-I relation were calculated for each combination of parameters and compared to the reference values. A total of 32,768 simulations were performed to evaluate each condition. In hyperexcitability, 571 simulations produced results that matched all electrophysiological changes observed in the experimental data from SOD-1 animal models reported in the literature. Most of the simulations (240) matched the experimental data when the Na⁺ and Ca⁺⁺ PICs were increased, whereas the slow K⁺ current and the length of the dendritic compartment were decreased. Similarly, in 116 simulations an increase of PICs and a decrease of slow K⁺ current were sufficient to reproduce the experimental findings. In the normal excitability condition, only 32 simulations were able to reproduce the experimental data. In these 32 simulations, the dendritic morphology had to be increased. Additionally, an increase of the slow K⁺ current was necessary for 13 simulations. Thus, the model represented two conditions observed in genetically modified animal models of ALS and provided additional evidence on the biophysical mechanisms operating in MN membrane during neurodegeneration. Future studies can include the MN model in a multi-scale neuromuscular model to investigate force control at the onset of ALS.

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 089.13/III41

Topic: I.06. Computation, Modeling, and Simulation

Support: NCCR Grant 565488

Title: A modeling and experimental framework to understand and optimize ultrasound neuromodulation

Authors: *T. LEMAIRE¹, F. DEDOLA², F. P. ULLOA SEVERINO³, A. CUTRONE², N. KUSTER^{4,5}, A. MAZZONI², V. TORRE³, E. NEUFELD⁴, S. MICERA^{1,2}

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Abstract: *Low-Intensity Focused Ultrasound Stimulation* (LIFUS) is a promising candidate to achieve non-invasive, local, and controllable modulation of neural activity. However, the fundamental mechanisms of action and the sub-cellular receptive structures at stake are still unclear, and the contrasting sensitivities of different central and peripheral neural structures to LIFUS has yet to be explained. Among the various theories of LIFUS-neuron interaction, the *Neuronal Intramembrane Cavitation Excitation* (NICE) model recently proposed by Plaksin et al.¹ provides quantitative predictions of cell-type-specific LIFUS-induced excitation mechanisms coherent with the results of numerous *in-vitro* and *in-vivo* studies.

Through a newly developed coarse-graining approach, it was possible to implement a NICE model variant that accurately captures the predicted millisecond-scale dynamics of cell-specific LIFUS neural responses, while accelerating computation times by more than three orders of magnitude. The resulting model facilitates (1) advance beyond point-neuron models to more realistic, spatially extended, morphologically and electrophysiologically detailed neuron models, (2) efficient exploration of large (stimulation and electrophysiology) parameter spaces, and (3) conveying of interpretable meaning to the combined mechanical-electrophysiological model in terms of effective channel gating and membrane current dynamics.

In parallel, we performed a series of experiments on single leech ganglion preparations. We could elicit reliable, direct excitation of the soma of sensory neurons through ultrasound, as measured by electrophysiology. Furthermore, spike analysis revealed a significant degree of similarity with the predicted behavior according to the NICE model, which differs in important ways from electromagnetic stimulation (e.g., stimulation vs. inhibition, bursting behavior, spike-

shape variability...). We now seek to validate the model from a mechanistic standpoint, using light-scattering techniques to directly detect and analyze LIFUS-induced mechanical oscillations in the plasma membrane of ganglionic neurons.

Building on these results, we are now developing a multiscale modeling framework that couples realistic models of LIFUS-neuron interaction to modeling of acoustic propagation in anatomical models, in order to provide guidance and optimization in the development of application - and patient - specific LIFUS-based neuromodulation therapies.

I. Plaksin, M., Shoham, S. & Kimmel, E. Intramembrane Cavitation as a Predictive Bio-Piezoelectric Mechanism for Ultrasonic Brain Stimulation. *Phys. Rev. X* 4, (2014).

Disclosures: T. Lemaire: None. F. Dedola: None. F.P. Ulloa Severino: None. A. Cutrone: None. N. Kuster: None. A. Mazzoni: None. V. Torre: None. E. Neufeld: None. S. Micera: None.

Poster

089. Computation, Modeling, and Simulation: Cellular Models

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 089.14/III42

Topic: I.06. Computation, Modeling, and Simulation

Support: R01EB021703

Title: Modeling the spatial inhomogeneous degradation of nitric oxide (NO) shows a key role of anatomically localized NO production

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Abstract: The interaction between neural activity and the hemodynamic response is known as neurovascular coupling (NVC). Understanding how changes in neural activity drive changes in blood flow is vital for the accurate interpretation of hemodynamic signals. While neurovascular coupling is thought to be mediated by many signaling molecules, here we focus on Nitric oxide (NO). NO is a potent vasodilator and neural activity modulator that freely diffuses across cell membranes. NO released from neurons dilates arteries, and is also rapidly degraded by interactions with hemoglobin (Hb) in the blood. The dynamics of NO-mediated NVC is dependent on the perivascular location and magnitude of NO production and degradation, as well as its diffusion through tissues. We used a computational model to simulate NO production, diffusion and degradation in a cortical column. The minimum NO production rate is set by a concentration sufficient to cause dilation of the smooth muscle, while the upper bound is set by NO concentrations that cause a toxic inhibition of aerobic respiration in cytochrome c oxidase

(CcO). We show that in order to generate physiologically plausible dilations without toxic inhibition of CcO, proximal production of NO is required. Additionally, we show that vessel size is an important factor in determining arteriole sensitivity to NO, as the amount of hemoglobin present in the vessel impacts the degradation rate of NO and can account for larger dilations in smaller arteries (as a percentage of resting vessel diameter) observed experimentally. We also investigate how NO-mediated NVC can be altered during hypoxia and when free hemoglobin levels in the plasma are pathologically elevated. Lastly, because NO also affects neural excitability, we investigated how vascular changes could impact NO concentrations in brain tissue. Our simulations show that the spatial arrangement of NO production plays a key role in determining the efficacy of NO on arteries and other tissues.

Disclosures: W.D. Haselden: None. R. Teja: None. P.J. Drew: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.01/III43

Topic: I.07. Data Analysis and Statistics

Support: Seed Grant from Stanford Department of Anesthesiology

Title: Remifentanil and nitrous oxide anesthesia produces a unique pattern of EEG activity during loss and recovery of response

Authors: *S. L. EAGLEMAN¹, C. DROVER⁴, D. DROVER², N. OUELLETTE², B. MACIVER³

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⁴Univ. of Washington, Seattle, WA

Abstract: Nitrous oxide (N₂O) and remifentanil (remi) are used along with other anesthetic and adjuvant agents for routine surgical anesthesia, yet the electroencephalogram (EEG) changes produced by this combination are poorly described. N₂O administered alone produces EEG spectral characteristics that are distinct from most hypnotics. Furthermore, EEG frequency-derived trends before and after clinically relevant time points vary depending on N₂O concentration. Remifentanil typically increases low frequency and decreases high frequency activity in the EEG, but how it influences the EEG effect of N₂O is not known. Previous attempts to characterize EEG signals of patients anesthetized with nitrous oxide using frequency-derived measures have shown conflicts and inconsistencies. Thus, in addition to determining the spectral characteristics of this unique combination, we also test whether a newly proposed characterization of time-delayed embeddings of the EEG signal tracks loss and recovery of consciousness significantly at clinically relevant time points. We retrospectively investigated the

effects of remi and N₂O on EEG signals recorded from 32 surgical patients receiving anesthesia for elective abdominal surgeries. Remifentanil and nitrous oxide (66%) were co-administered during the procedures. Patients were tested for loss and recovery of response to verbal stimuli after induction and upon cessation of anesthesia, respectively. We found that the addition of remifentanil to nitrous oxide anesthesia improves the ability of traditional frequency-derived measures, including the Bispectral Index (BIS), to discriminate between loss and recovery of response. Finally, we found that a novel analysis of EEG that characterizes time-delayed embeddings showed more significant differences between states than most spectral measures.

Disclosures: **S.L. Eagleman:** None. **C. Drover:** None. **D. Drover:** F. Consulting Fees (e.g., advisory boards); DD is a consultant for Masimo, Inc.. **N. Ouellette:** None. **B. MacIver:** None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.02/III44

Topic: I.07. Data Analysis and Statistics

Title: Modulation analysis of evoked potentials related to auditory-visual integration

Authors: ***M. E. PFLIEGER**^{1,2}, L. GAO¹

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Abstract: *Motivation.* We aim to study auditory-visual integration processes in humans via an experimental analysis framework that generalizes auditory and visual evoked potential (AEP, VEP) measurements. AEPs and VEPs, measured by averaging EEG epochs aligned to single events, reflect 1st-order brain responses to stimuli. However, auditory-visual integration requires at least two events that interact via higher-order brain processes. This exploratory study applied the Volterra-Hansen theory [1] to analyze, for the first time, auditory modulation of VEPs and visual modulation of AEPs using a task that required combined information from both modalities.

Experiment. One of us (LG) volunteered to undergo 128-channel EEG while performing a task to press a button for conjunctions of auditory stimuli (1000 Hz or 1500 Hz 40 ms tone pips) and visual stimuli (letters "L" or "H", 33 ms) that were "congruent" (both "low" = "L" + 1000 Hz; or both "high" = "H" + 1500 Hz), and to refrain from responding to "incongruent" conjunctions ("L" + 1500 Hz; or "H" + 1000 Hz). All stimuli and combinations were equally probable and independent. An A-V trial comprised an auditory stimulus followed by a visual stimulus (trimmed Poisson SOA, $\lambda = 150$ ms; uniform ITI, 2500 ms to 3000 ms), and vice versa for V-A trials. The experiment comprised a series of 8 5-minute runs of trials (4 A-V, 4 V-A). Incongruent (no-response) trials were analyzed.

Analysis. Preprocessed, paired-stimulus (S1-S2) epochs (500 ms before S1, 1500 ms after S2) were analyzed in 2 stages via the frequency domain methods of [1]. Stage 1 derived 1st-order EP-like kernels for S1 and S2. After subtracting 1st-order (S1,S2)-aligned kernels from each epoch, stage 2 derived a 2nd-order kernel for the S1-modulation of S2.

Results. Analysis of A-V runs revealed a prominent series of modulations 182 ms post-V ranging from +4 μ V for 30 ms SOAs to -4 μ V for 300 ms SOAs; topography suggested left fusiform gyrus generation. Spatial ICA (50-500 ms post-A) of V-A modulations revealed a ~40% variance component peaking ~400 ms that suggested superior temporal gyrus generation.

Conclusion. This preliminary study suggests that the generalized EP experimental analysis framework is feasible, and it generated specific hypotheses related to the asymmetry of auditory-then-visual vs. visual-then-auditory integration processes. Trials with button presses would need analysis with 3-event epochs (S1, S2, R). A future study shall assess the test-retest reliability of EP modulations within participants across sessions.

Reference:

[1] Pflieger ME. Volterra-Hansen theory of event-related transients modulated by inter-event intervals. IJBEM. 2011;14(1):34-9.

Disclosures: **M.E. Pflieger:** A. Employment/Salary (full or part-time):: Cortech Solutions, Inc. **L. Gao:** A. Employment/Salary (full or part-time):: Cortech Solutions, Inc..

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.03/III45

Topic: I.07. Data Analysis and Statistics

Support: Swiss National Science Foundation

Title: A framework for realistic simulation of EEG scalp signals using MRI-based forward models and biologically plausible models of neural signal and noise

Authors: ***E. BARZEGARAN**, P. J. KOHLER, A. M. NORCIA
Stanford Univ., Stanford, CA

Abstract: Electroencephalography (EEG) is widely used to investigate brain function. EEG simulation studies are useful for assessing the validity of analysis methods and the interpretability of results. These studies typically use average head models and linear signal models when modeling scalp responses despite substantial individual differences in cortical geometry and evidence of nonlinearities in brain dynamics. Here we address these limitations with a highly realistic simulation environment that incorporates variability in individual anatomy and employs biologically plausible models of signal and noise. This model can be used for

evaluation and validation of a wide range of EEG analysis tools including pipelines for source localization, functional connectivity, and signal decomposition. We use individual head models extracted from MRI images to generate surface-based forward solutions. A set of regions-of-interest (ROIs) from whole brain (Glasser et al., 2016) and visual cortex (Wang et al., 2015) atlases is brought into registration with the brain of each individual using surface-based alignment. EEG dynamics are simulated using realistic noise and signal models and the signal-to-noise ratio (SNR) can be varied. The noise model has three components: (1) background activity: spatially coherent 1/f noise with a spatial decay in coherence distributed over the cortical sources, (2) alpha activity: alpha-shaped Gaussian noise within visual ROIs, and (3) measurement noise added at the sensor level. The signal is implemented at the source level within the ROIs and can be generated in two ways: Steady state signals useful for evaluating of EEG decomposition and source imaging methods, and signals generated using linear and nonlinear autoregressive moving average models, useful for evaluating functional connectivity analyses. The flexibility to realistically model distinct types of signals in a wide range of brain areas, and with variable SNR, makes our framework a robust tool for EEG-based methodology assessment. We plan to further extend this framework by adding quantitative metrics that allow users to evaluate the accuracy of their source imaging methods and functional connectivity estimations by comparing them to the original source signal model. All the code, including noise and signal modeling and visualization tool, as well as individual forward solutions and ROIs will be made freely available to the scientific community.

References

Glasser, et al. "A multi-modal parcellation of human cerebral cortex" *Nature* 536.7615 (2016): 171-178
Wang, et al. "Probabilistic maps of visual topography in human cortex" *Cerebral cortex* 25.10 (2014): 3911-3931

Disclosures: E. Barzegaran: None. P.J. Kohler: None. A.M. Norcia: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.04/III46

Topic: I.07. Data Analysis and Statistics

Title: Controlling robot by electroencephalograms on recalling images of its movement

Authors: *T. YAMANOI¹, H. TAKAYANAGI², H. TOYOSHIMA³, T. YAMAZAKI⁴, M. SUGENO⁵

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⁴Kyushu Inst. of Technol., Fukuoka, Japan; ⁵Emeritus Professor, Tokyo Inst. of Technol., Tokyo, Japan

Abstract: The paper is concerned with brain machine interface to control a robot. We measured electroencephalograms (EEGs) when three subjects were recognizing and, then, recalling, i.e., imaging the ten movements of a robot displayed on a PC monitor. Then we analyzed EEGs by using three different groups of sampling data collected at different latencies with the same sampling period. The obtained data are considered as 84 dimensional vectors. The number of external criteria is 10: the number of different robot movements and that of explanatory variables is 84: EEG data. The canonical discriminant analysis was applied to triple sampled single-trial-EEGs. The results were obtained by applying the jack knife algorithm, where discrimination ratio was found to be 100% for each of three subjects. Then, the discriminant results were transmitted to the robot PLEN by Wi-Fi. We found that the robot was successfully controlled with the ten commands obtained by single-trial-EEGs taken from the subjects when they were just recalling the images of robot's movement.

Disclosures: **T. Yamanoi:** None. **H. Takayanagi:** None. **H. Toyoshima:** None. **T. Yamazaki:** None. **M. Sugeno:** None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.05/III47

Topic: I.07. Data Analysis and Statistics

Support: Brazilian National Council for Scientific and Technological Development (CNPq) grant (206907/2014-1)

Title: Do seizures have a characteristic timescale for detection?

Authors: ***L. SOUZA FRANCA**¹, M. C. WALKER¹, Y. WANG²

¹Dept. of Clin. and Exptl. Epilepsy, Univ. Col. London, London, United Kingdom; ²Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: Epilepsy is still a cause of impairment to millions of people around the world. Even infrequent seizures have an enormous impact on quality of life due to their unpredictability. However, reliable seizure detection and prediction remains a challenge. Over the last few years, advanced signal processing techniques have been applied to the study of electroencephalographic (EEG) signals and emergence of epileptic seizures. Nevertheless, more fundamental questions, such as optimal timescale and sampling frequency in order to detect relevant processes generating and modulating seizures, have not received much attention to date.

We propose an evaluation of the impact of both epochs sizes (timescale) and sampling frequency of EEG signals around epileptic seizures. We applied the Chhabra-Jensen multifractal approach to signals recorded invasively from three patients undergoing epilepsy surgery pre-evaluation. These signals were initially recorded at a sampling rate of 5000Hz and then downsampled in 15 different sampling rates, ranging from 5000Hz to 250Hz. The epochs' size were set to the values: 1024, 2048, 4096, and 8192 datapoints. As an initial investigation, Cohen's D was obtained for the multifractal spectral properties comparing ictal and interictal distributions. Cohen's D values show the existence an optimal time scale to detect changes around seizures. This optimal time scale varies slightly between patients. The results suggest that there may be an optimal timescale for detecting changes in processes generating or modulating an epileptic seizure, and that this time scale may be specific for each patient.

Disclosures: L. Souza Franca: None. M.C. Walker: None. Y. Wang: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.06/III48

Topic: I.07. Data Analysis and Statistics

Support: NIH/NIGMS 1P01-GM118629-01A1 (E.N.B.)

Funds from Picower Institute for Learning and Memory (E.N.B., S.C., P.K.)

Picower postdoctoral fellowship (S.C.)

Title: A hidden Markov model for estimating burst suppression states

Authors: *S. CHAKRAVARTY¹, T. BAUM⁴, J. AN^{2,5}, P. KAHALI^{6,1}, B. WESTOVER⁶, E. N. BROWN^{1,2,6,3}

¹The Picower Inst. for Learning & Memory, ²Dept. of Brain and Cognitive Sci., ³Inst. of Med. Engin. and Sci., MIT, Cambridge, MA; ⁴Penn State Univ., University Park, PA; ⁵Duke-NUS Med. Sch., Natl. Univ. of Singapore, Singapore, Singapore; ⁶Dept. of Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hosp., Boston, MA

Abstract: Burst suppression is an electroencephalogram (EEG) pattern associated with profoundly inactivated brain states such as hypothermia, coma and general anesthesia, all characterized by cerebral metabolic depression. This pattern is distinguished by short-duration band-limited electrical activity (Bursts) interspersed between relatively near-isoelectric periods (Suppressions). A feature of burst suppression, utilized to monitor patients in a clinical setting, is that lengths of suppressions rise with increase in brain inactivation. To track this feature, in previous work our group established the Burst Suppression Probability (BSP) which is estimated from EEG using a state-space (SS) framework. A key improvement on this framework would be

to incorporate the idea from neuroscience that recovery of a burst from a suppression or vice versa could be dictated by dynamics of metabolic activity in brain. For example, a general observation that a suppression is sustained across a finite number of time-windows until a burst reappears can be translated into a statement that the likelihood to switch out of a suppression rises with longer time spent in the suppression and this time-varying probability could be a reflection of the underlying metabolic dynamics. With this motivation, we propose a novel algorithmic framework with which we can develop models that relate probability of switching out of a burst/suppression to the duration spent in that state. Our framework is based on a Hidden Semi-Markov Model - a type of Hidden Markov Model (HMM) wherein the state transition matrix (STM) depends on the duration spent in the current state. We postulate that, at any given time-window, there exists one of two possible states - a burst or a suppression, either of which generates the observations. This way of posing the problem enables us to estimate the posterior distribution, given data and model parameters, on the joint space of the two states and the duration spent in each state. We pose the semi-Markov problem as a classical HMM problem and apply relevant tools available for HMMs to the current problem in three ways: (1) to filter the noisy data and identify underlying burst/suppression segments, (2) to estimate the most likely sequence of states, and (3) to estimate HMM parameters, e.g. the STM. We demonstrate our framework using both synthetic and clinical data. Since the STM in this framework captures the duration-dependence of the states' propensity to transition, the analysis of STMs estimated from disjoint data segments can provide insights into developing a more realistic SS model to track the brain's metabolic state during burst suppression.

Disclosures: **S. Chakravarty:** None. **T. Baum:** None. **J. An:** None. **P. Kahali:** None. **B. Westover:** None. **E.N. Brown:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Masimo. **E. Ownership Interest** (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Masimo.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.07/III49

Topic: I.07. Data Analysis and Statistics

Support: The Thailand Research Fund under Grant MRG6180028

Title: Opening the gate to continuous SSVEP-based BCIs

Authors: ***T. WILAI PRASITPORN**¹, X. DU², F. KOEGL³, N. BANLUESOMBATKUL¹, P. MANOONPONG¹, T. YAGI²

¹Vidyasirimedhi Inst. of Sci. and Technol., Rayong, Thailand; ²Tokyo Inst. of Technol., Tokyo, Japan; ³Munich Sch. of Engin., Munich, Germany

Abstract: Electroencephalography (EEG)-based brain-computer interfaces (BCI) have been an active research issue for over three centuries. Recent massive improvements of electronic components and computational resources make BCIs very fascinating to researchers at this moment. So far, most EEG-based BCIs have used discrete information to activate/control devices, but not continuous information for smooth and continuous control applications, such as robot motion control. Achieving an EEG-based BCI with continuous information remains a great challenge. There are several types of the state-of-the-art EEG-based BCIs. In this study, we focused on developing the steady state visual evoked potential (SSVEP)-based BCI for continuous and smooth brain-machine interaction. To achieve this, we proposed a variation of the visual stimulus intensity (at constant flickering frequency) as a visual cue in assisting human participants to control the magnitude of their respective SSVEP responses. Experimental studies on eleven healthy participants revealed that by continuously increasing or decreasing the stimulus intensity, the trending of the SSVEP responses can be controlled. Polynomial and exponential curve fittings were used to obtain characteristics of the controlled SSVEP responses. The quantitative measures root-mean-square error and R-squared show that polynomial curve fittings with degree three are the best approximations of the curve of the control SSVEP. Thus, we continued using polynomial regression with degree three for modelling the transfer functions between the stimulus intensity and the SSVEP responses. The outcomes of this polynomial regression model can be vital in designing stimulation for continuous SSVEP-based BCI applications. Finally, we also executed a cross-participant validation on the developed model to predict the visual stimulus intensity from input SSVEP responses. Continuous increasing or decreasing of the predicted stimulus intensity can be mapped into command functions for smooth brain-controlled machines. The results were promising and open up a new way of achieving continuous BCI-based control applications instead of the traditional discrete ones.

Disclosures: **T. Wilaiprasitporn:** 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.; The Thailand Research Fund under Grant MRG6180028. **X. Du:** None. **F. Koegl:** None. **N. Banluesombatkul:** None. **P. Manoonpong:** None. **T. Yagi:** None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.08/III50

Topic: I.07. Data Analysis and Statistics

Title: Universal spike classification

Authors: *M. SAIF-UR-REHMAN¹, R. LIENKÄMPER¹, Y. PARPALEY¹, T. GLASMACHERS², C. LIU³, B. LEE³, S. KELLIS⁴, R. ANDERSEN⁴, C. KLAES¹

¹Dept. of Neurosurgery, Knappschaftskrankenhaus Bochum, ²Inst. of Neuroinformatics, Ruhr Univ., Bochum, Germany; ³Neurorestoration Ctr. and the Dept. of Neurosurg. and Neurol., USC, Los Angeles, CA; ⁴Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: In electrophysiology, microelectrodes are the primary source for recording neural data (single unit activity). These microelectrodes are implanted individually, or in the form of tiny but dense microelectrode arrays, consisting of hundreds of channels. During recording, some channels capture the activity of neural units which is usually contaminated with noise and/or artifacts. Another considerable fraction of channels does not record any neural data, but only external artifacts and/or noise. Furthermore, some units are lost from a channel, or a new unit can appear on a channel during the recording. Therefore, an automatic identification and monitoring of the channels containing neural data can accelerate the process of analysis, e.g., automatic selection of meaningful channels during offline spike sorting. Here, we propose a novel algorithm based on supervised machine learning, a universal spike classifier (USC), that enables us to address both the above-raised issues. The USC uses a state-of-the-art deep neural network architecture. It takes a batch of preprocessed waveforms as input, propagates it through multiple layered structures, and finally classifies it as a channel containing neural spike data or only artifacts/noise. We have trained the model of USC on data recorded from a single tetraplegic patient with two Utah arrays implanted in different areas of brain. The trained model was then evaluated on preliminary data, collected from five epileptic patients implanted with depth electrodes and two tetraplegic patients implanted with Utah arrays, separately. The implanted electrodes targeted different areas of the brain. The test accuracy was 96.73% on more than half a million (530833) of inputs, collected from all seven patients. This result demonstrates that USC generalizes not only to the new data, but also to brain areas, subjects, and electrodes not used for training. This underlines the universality of the proposed spike classifier.

The present study shows that the USC can detect and track channels containing neural data, universally. However, it is possible that the detected neural channel captures data from more than one neural unit. In the future, we aim to extend the method to detect and track every present neural unit individually and universally.

Disclosures: M. Saif-ur-Rehman: None. R. Lienkämper: None. Y. Parpaley: None. T. Glasmachers: None. C. Liu: None. B. Lee: None. S. Kellis: None. R. Andersen: None. C. Klaes: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.09/III51

Topic: I.07. Data Analysis and Statistics

Title: Exploring mental state changes during hypnotherapy using adaptive mixture independent component analysis

Authors: *Y. ZI, S.-H. HSU, Y. WU, T.-P. JUNG
Swartz Ctr. for Computat. Neuroscience, INST, La Jolla, CA

Abstract: A significant challenge to brain-state monitoring in clinical or brain-computer interfaces (BCI) contexts is effective decoding of underlying cognitive or mental states and quantitative assessment of state changes. This study explores new computational tools for decoding brain states from continuous, unlabeled electroencephalogram (EEG) and obtaining insights into source network dynamics that contribute to state changes. In particular, adaptive mixture independent component analysis (AMICA) is an unsupervised-learning approach that solves for a mixture of distinct ICA models - each representing a different set of statistically independent sources - to characterize active brain networks under different cognitive states. This study applies AMICA to 5 sessions of EEG data collected from 2 adults during Healing Light Guided Imagery (HLGI). HLGI - and other forms of guided imagery hypnotherapy (GIH) - involve guiding participants through relaxation, then a light, self-induced trance, during which self-affirming imagery is explored. Empirical results show that AMICA can effectively characterize mental-state changes across various phases of hypnotherapy sessions. The source compositions and activities of each ICA model revealed active brain networks associated with different hypnotherapy stages. The generalizability of the findings across sessions and subjects is examined. AMICA thus provides an effective data-driven approach that learns interpretable models for exploring underlying cognitive or mental states changes from continuous, unlabeled EEG data.

Disclosures: Y. Zi: None. S. Hsu: None. Y. Wu: None. T. Jung: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.10/III52

Topic: I.07. Data Analysis and Statistics

Title: Effect of filter's cutoff frequencies and ICA on the amplitudes of somatosensory evoked potentials

Authors: *M. NAVID^{1,2,4}, I. K. NIAZI^{4,5,3}, D. LELIC¹, A. M. DREWES^{1,2}, H. HAAVIK⁴
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Abstract: Objective:

Somatosensory evoked potentials (SEPs) are used frequently in clinical settings. The literature review of studies from the past 17 years in which SEPs are analyzed, showed inconsistency in methods used for preprocessing SEPs, especially filter's cutoff frequencies. The objective of this study was to determine the effects of different filter pass-band frequencies and application of ICA to clean data on the amplitudes of SEPs.

Method:

68 datasets from 17 healthy volunteers (age range 19-36 years) were included in the study. The right median nerve of the participants was stimulated 1000 times with a square pulse of width 1ms and frequency 2.3Hz. The EEG was recorded from 62 channels, sampled at 2048Hz, which was average referenced offline. Six methods were used to preprocess EEG. These combinations were made from 3 cutoff frequencies of 2nd order Butterworth filter (i)0.5-1000Hz, (ii)3-1000Hz and (iii)30-1000Hz; and whether ICA was applied or not. Continuous EEG was epoched from -100ms to 150ms with respect to stimulation. After rejecting bad epochs, ICA was used to correct line noise, eye, and EMG artifacts. The amplitude was measured from the baseline corrected averaged epochs (channel F3) by taking the absolute difference of P22 and N30.

Results:

Friedman test showed significant interaction between filter cutoff frequencies and ICA on the amplitude of N30 ($\chi^2(5)=219$; $p<0.001$). Dunn-Bonferroni post-hoc tests revealed that amplitude of N30 is significantly affected by the use of (i) ICA with 0.5-1000Hz, and 3-1000Hz bands; and (ii) 30-1000Hz frequency band compared to 0.5-1000Hz and 3-1000Hz bands, irrespective of whether ICA is used or not to clean the data.

Conclusion/Significance:

Different preprocessing methods significantly altered the amplitude of SEPs. This implies there is a need to standardize preprocessing method for analyzing SEPs, as this will lead to the reproducibility and comparison of studies.

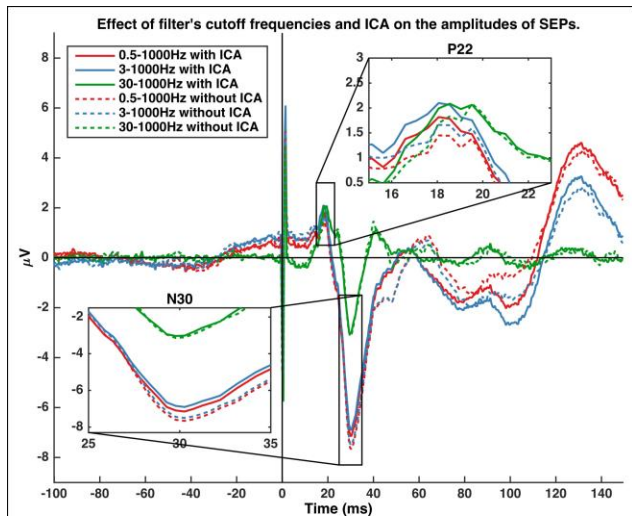


Figure: SEPs from a representative participant, processed with 2nd order Butterworth filter with three different pass-bands (i) 0.5-1000Hz, (ii) 3-1000Hz and (iii) 30-1000Hz in combination with and without application of ICA. The N30 amplitude was measured from baseline corrected averaged epochs at channel F3 as peak-to-peak from the amplitude of the positivity (P22) preceding the N30 to the amplitude where N30 was the highest. The amplitude of N30 is significantly affected by the use of (i) ICA with 0.5-1000Hz (with ICA vs without ICA; $p < 0.003$), and 3-1000Hz (with ICA vs without ICA; $p < 0.001$) bands, as can be seen here by comparing same colored (except green which represents 30-1000Hz band) solid and dashed lines; and (ii) 30-1000Hz frequency band compared to 0.5-1000Hz and 3-1000Hz bands, irrespective of whether ICA is used or not to clean the data (all $p < 0.001$), which can be easily seen in the inset figure N30 (bottom-left). The inset figures, P22 (top-right) and N30 (bottom-left), give more insight to these difference in amplitudes among differently processed SEPs.

Disclosures: M. Navid: None. I.K. Niazi: None. D. Lelic: None. A.M. Drewes: None. H. Haavik: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.11/DP14/III53

Topic: I.07. Data Analysis and Statistics

Support: NRC IRAP 875781
OCE TalentEdge 26529

Title: Low cost, high throughput EEG & ERP research with a sparse wearable system

Authors: *G. MOFFAT, N. PROULX, H. J. BANVILLE, C. AIMONE
Interaxon, Toronto, ON, Canada

Abstract: Muse is a portable 4 (or 5) channel device now widely used in neuroscience research on ERPs, single trial classification, hemispheric asymmetry, VR, population dynamics,

neurofeedback, numerous other paradigms, in clinical neurofeedback, and in neuroscience education at all levels. While some EEG and ERP researchers have questioned the utility of ultra-low-cost EEG systems in research, we demonstrate that Muse produces robust ERPs in classic paradigms, requiring 10-12 minutes per subject from setup to completion. We also show that remote, app-based longitudinal data collection with Muse generates useful, extremely large scale population level EEG data, which may have broad utility in neuroscience and brain health research. We show that other physiological signals such as electrocardiography (ECG), ballistocardiography (BCG) and respiration are robustly measurable with Muse, and describe how low-cost EEG and ERP based on Muse can be integrated into different wearable form factors, including sunglasses and VR/AR headsets.

We describe a suite of open source and low cost software tools that enable data collection and analysis with Muse, including mobile and desktop applications, cloud storage and file conversion, integration of Lab Streaming Layer, tools for ERP experimentation and analysis in python and iOS. We further describe a platform for scalable, unsupervised, longitudinal collection of remote EEG data from subjects at home or outside the lab, and describe its use neurofeedback or clinical mental health practice.

The features and performance of the Muse ecosystem were tested in different scenarios using these tools:

Study 1. We assessed data quality and ease of use for remote EEG, via signal characteristics and session user experience metrics, on a small (1,118,000 sessions) subset of total individual user sessions, and describe how this unique data resource can inform new paradigms in neuroscience research.

Study 2. ERPs in an auditory and visual oddball task and a face/house paradigm are described, along with performance of single-trial classification using a Riemannian geometry based feature classifier pipeline.

Study 3. ECG (electrocardiogram) and BCG (ballistocardiogram) were recorded with Muse and are described herein, revealing a small mean absolute error in heart rate of 2.1 BPM, and suggesting that BCG measured on head provides a reliable estimate of some parameters of cardiac physiology.

Disclosures: **G. Moffat:** A. Employment/Salary (full or part-time); Interaxon Inc. **N. Proulx:** A. Employment/Salary (full or part-time); Interaxon. **H.J. Banville:** A. Employment/Salary (full or part-time); Interaxon. **C. Aimone:** A. Employment/Salary (full or part-time); Interaxon. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Interaxon.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.12/III54

Topic: I.07. Data Analysis and Statistics

Support: DFG, EXC 1086

Title: Relation of local field potentials and multi-unit activity during interictal epileptic activity

Authors: *M. GLASTETTER, E. LIZANA, A. SCHULZE-BONHAGE, T. BALL
Univ. Med. Ctr., Freiburg im Breisgau, Germany

Abstract: Microelectrode recordings allow for the simultaneous quantification of the activity of small neuronal ensembles (multi-unit activity, MUA) and Local Field Potentials (LFPs). So far it is still unclear to what extent MUA (>500 Hz) contributes to the generation of the LFP (<500 Hz). It has been proposed that the relation between these different scales varies depending on the underlying neuronal morphology, the synaptic distribution and the correlation of synaptic activity.

In the current study 3 patients with intractable epilepsy were visually examined for interictal epileptic discharges in the parahippocampus. We were able to reproduce findings from a physiological study on microelectrode recordings from the hand region of macaque somatosensory cortex [1], in which a strong correlation of averaged high-gamma power over frequency bands in LFP and average firing rate was revealed. Our findings, derived from pathophysiological events, suggest a correlation that is not only predominant in the frequency band between 60 Hz and 150 Hz, but also extends to frequency bands as high as 500 Hz (see Fig 1B). We were further able to show that MUA and spectral power of the LFP in certain frequency bands significantly correlate (Spearman rank correlation, FDR corrected $q=0.05$) on a trial-by-trial basis (see Fig 1A).

Our findings show that microrecordings can reveal new aspects about the behavior of epileptic networks. Further, the correlation of high-gamma power in LFP with average firing rate is in accordance with previous findings in monkeys, but not necessarily in the same frequency range. [1] RAY, Supratim, et al. Neural correlates of high-gamma oscillations (60-200 Hz) in macaque local field potentials and their potential implications in electrocorticography. *Journal of Neuroscience*, 2008, 28. Jg., Nr. 45, S. 11526-11536.

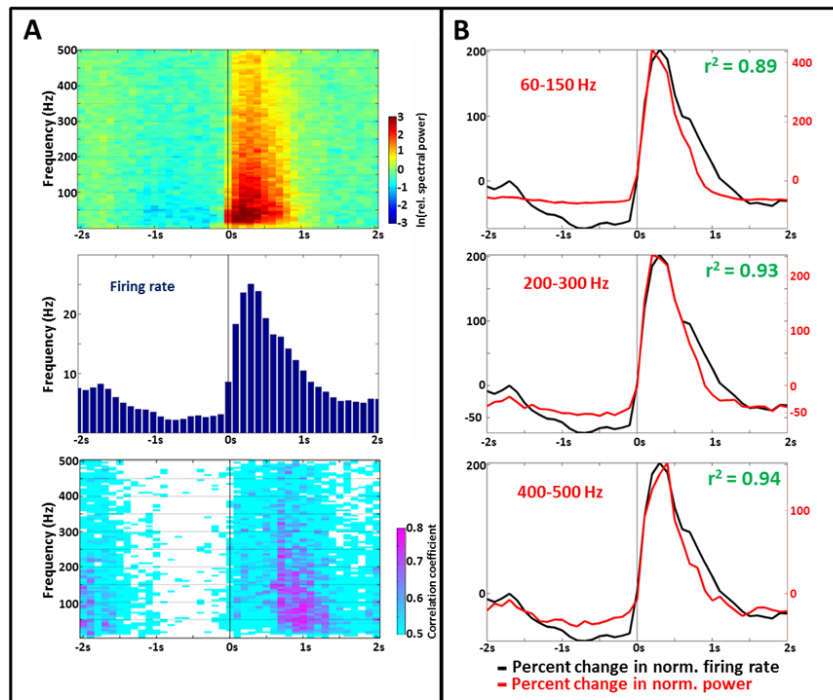


Figure 1:

A Upper panel: Averaged time-frequency plot of interictal epileptic bursts. There is a clear increase in power after spike onset at 0s. Middle panel: Trial-averaged spike rate. The spike rate increases after spike onset in accordance with increase in power (see upper panel). Lower Panel: Corresponding (to upper panel) trial-based rank correlation coefficients (FDR corrected, $q=0.05$) of power vs. action potential rate.

B Correlation (see r^2 , depicted in green) between firing rate (MUA, depicted in black) and change in spectral power (depicted in red) for three different frequency bands

The figures show exemplary results from a microelectrode, implanted in the left mesial parahippocampus.

Disclosures: M. Glastetter: None. E. Lizana: None. A. Schulze-Bonhage: None. T. Ball: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.13/III55

Topic: I.07. Data Analysis and Statistics

Support: KreutzKamp TMS RES F- 2467
NSF IIP-1719130
ARL W911NF-10-2-0022
NIH R01 NS047293-13A1
The Swartz Foundation

Title: Modeling brain dynamic state changes with adaptive mixture independent component analysis

Authors: *S.-H. HSU¹, L. PION-TONACHINI¹, J. A. PALMER², M. MIYAKOSHI¹, S. MAKEIG¹, T.-P. JUNG¹

¹Swartz Ctr. for Computat. Neuroscience, Inst. for Neural Computation, Univ. of California San Diego, LA Jolla, CA; ²Inst. for Neural Computation, Osaka Univ., Osaka, Japan

Abstract: There is a growing interest in neuroscience in assessing the continuous, endogenous, and nonstationary dynamics of brain network activity supporting the fluidity of human cognition and behavior. This non-stationarity may involve ever-changing formation and dissolution of active cortical sources and brain networks. However, to date there has been no unsupervised approach to identify and model these changes in brain dynamics as continuous transitions between quasi-stable brain states using unlabeled, noninvasive recordings of brain activity. This study explores the use of adaptive mixture independent component analysis (AMICA) to model multichannel electroencephalographic (EEG) data with a set of ICA models, each of which decomposes an adaptively learned portion of the data into statistically independent sources. We first show that AMICA can segment simulated quasi-stationary EEG data and accurately identify ground-truth sources and source model transitions. Next, we demonstrate that AMICA decomposition, applied to 6-13 channel scalp recordings from the CAP Sleep Database, can characterize sleep stage dynamics, allowing 75% accuracy in identifying transitions between six sleep stages without use of EEG power spectra. Finally, applied to 30-channel data from subjects in a driving simulator, AMICA identifies models that account for EEG during faster and slower response to driving challenges, respectively. We show changes in relative probabilities of these models allow effective prediction of subject response speed and moment-by-moment characterization of state changes within single trials. AMICA thus provides a generic unsupervised approach to identifying and modeling changes in EEG dynamics. Applied to continuous, unlabeled multichannel data, AMICA may likely be used to detect and study any changes in cognitive states.

Disclosures: **S. Hsu:** None. **L. Pion-Tonachini:** None. **J.A. Palmer:** None. **M. Miyakoshi:** None. **S. Makeig:** None. **T. Jung:** None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.14/III56

Topic: I.07. Data Analysis and Statistics

Support: RO1HD073254
5RO1EB009048

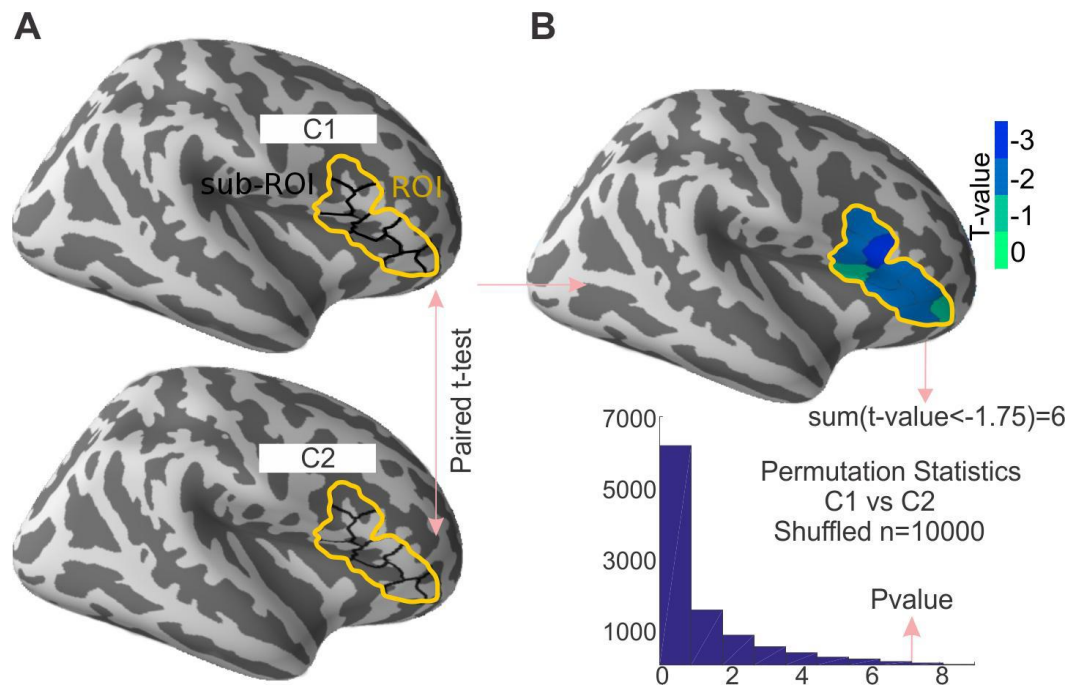
Title: A novel approach to enhance statistical power for regions of interest based analysis in eeg and meg data

Authors: ***F. MAMASHLI**¹, **M. HAMALAINEN**³, **T. KENET**⁴, **S. KHAN**²

¹Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Boston, MA; ²Massachusetts Gen. Hosp., Charlestown, MA; ³Massachusetts Gen. Hosp., Harvard Med. Sch., Charlestown, MA; ⁴Massachusetts Gen. Hosp, Charlestown, MA

Abstract: Electroencephalography (EEG) and magnetoencephalography (MEG) data are unique in their ability to provide neurophysiologically meaningful spectral and temporal information non-invasively. This rich content of the MEG/EEG data, increases the challenges and interpretation of the data in general and in connectivity analysis in particular. Many MEG/EEG studies address this complexity by using a hypothesis-driven approach, which focuses on particular regions of interest (ROI). However, if an effect is distributed unevenly over a large ROI, it may not be detectable using the conventional methods. Here, we propose a novel approach, which is based on the fact that if we divide each ROI into sub-ROIs, the effect of interest will remain similar. A non-parametric permutation method is then used to correct for multiple comparisons across sub-ROIs. The new approach is called PSR, which stands for *Permutation Statistics for ROI analysis*.

An example of an ROI and sub-ROI is in Figure 1A. PSR can be employed for various situations such as correcting for multiple comparisons in ROIs in the source space, inter-measure correlations and more importantly, connectivity analysis. A schematic of analyzing steps of PSR application in source space activity comparison is shown in Figure 1. We performed simulations to test the validity of the method on the connectivity analysis, as this is the most complicated scenario. Our simulations demonstrated that PSR enhances the contrast to noise ratio of the effect of interest and maximize the statistical power for weak and spatially discontinues effects. This results in the ability to identify statistically significant patterns with enhanced spectral, temporal, and spatial specificity. In addition, PSR were applied to the real, auditory mismatch, data set, which found stronger functional connectivity for deviant than standard tones around 200 ms in time and 20-40 Hz in frequency. We believe that PSR will play an important role in neuroscience studies by offering a novel way to detect functionally relevant patterns, hidden in the multifaceted MEG/EEG data.



Disclosures: F. Mamashli: None. M. Hamalainen: None. T. Kenet: None. S. Khan: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.15/III57

Topic: I.07. Data Analysis and Statistics

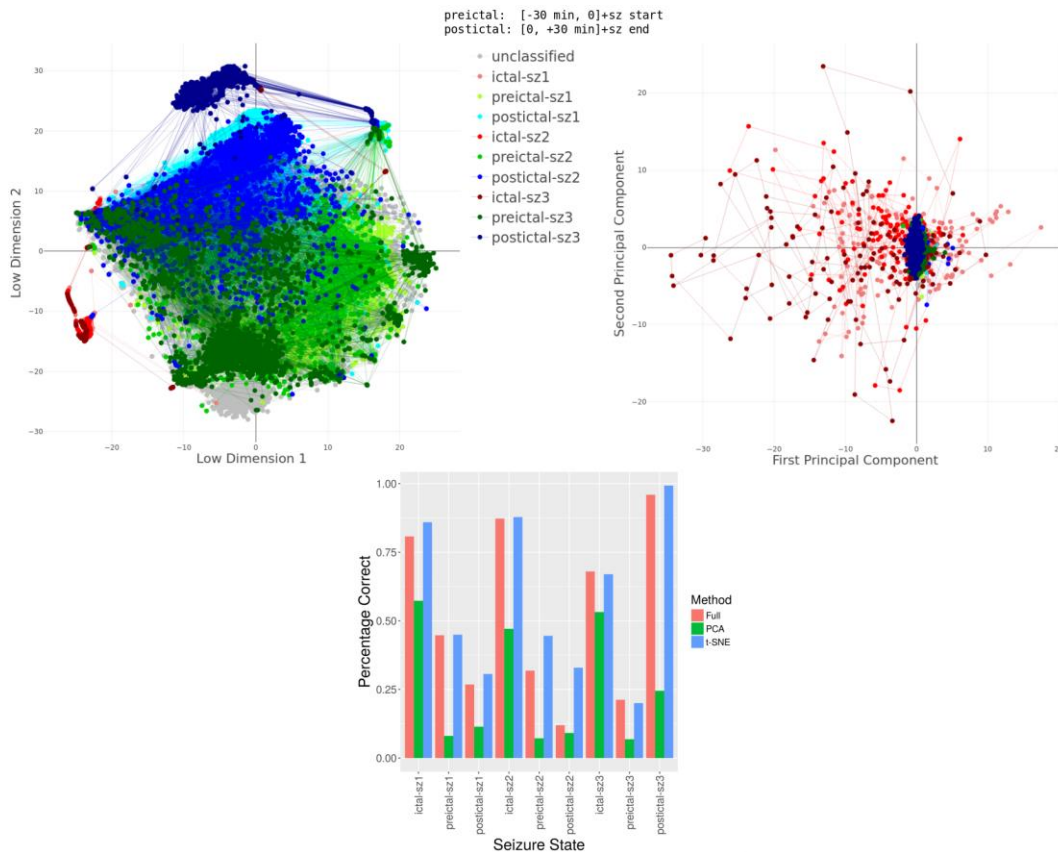
Support: NIH/NINDS R01NS079533

U.S. Department of Veterans Affairs, Merit Review Award RX000668

Title: Uncovering the low-dimensional structure of high-dimensional electrophysiological recordings in epilepsy

Authors: *J. RAPELA, T. PROIX, D. TODOROV, W. TRUCCOLO
Neurosci., Brown Univ., Providence, RI

Abstract: Advances in neural recording technology and signal processing now yield very high-dimensional descriptors of brain activity. However, the essential process of visual inspection in a high-dimensional space can become too challenging. Thus, it is useful to derive low-dimensional representations, especially in applications to neurological disorders. We are evaluating methods for such representations; e.g., t-distributed stochastic nonlinear embedding (t-SNE), hidden Markov models, principal components analysis (PCA). Here, we focus on t-SNE. Recordings from a 10x10 (4x4 mm²) microelectrode array, intracortically implanted in a patient with focal epilepsy, were segmented in 1 s time windows, represented in a high-dimensional space (2,072 features related to LFP power spectra, multi-unit activity (MUA) counts and their correlation matrix), and projected to low-dimensional spaces via t-SNE and PCA. Coordinates of points in Fig. 1a are t-SNE features from a recording segment including three "spike-and-wave" seizures (colors indicate preictal, ictal, and postictal states; shades mark different seizures; lines connect temporally adjacent time windows). Qualitatively, different states appear well separated, transitions between states are not gradual but abrupt, and ictal features are highly stereotypical (i.e., different from non-ictal ones and similar across seizures). In contrast, PCA failed to separate non-ictal features (Fig. 1b). We quantified the quality of low-dimensional representations by classifying (k-nearest-neighbors) time windows from a given seizure and state (e.g., ictal windows from seizure 1) using labeled data from all the other seizures and states. In all cases, t-SNE performed better than PCA. Classification accuracy using t-SNE was comparable to, and sometimes better than, that using the full high-dimensional representation (Fig. 1c). Hence, t-SNE low-dimensional representations appear useful for visualizing and classifying high-dimensional epileptic recordings, preserving relevant information and possibly eliminating noise.



Disclosures: J. Rapela: None. T. Proix: None. D. Todorov: None. W. Truccolo: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.16/III58

Topic: I.07. Data Analysis and Statistics

Support: NIMH grant R01MH087450

Title: Improving data quality and noise assessment in EEG signals: Bootstrapped standard error as a general and principled method

Authors: *A. X. STEWART, S. J. LUCK

Ctr. for Mind and Brain, Univ. of California, Davis, Davis, CA

Abstract: In EEG and ERP research, we are searching for small signals embedded in noise. The signal-to-noise ratio is key in designing good experiments and in data analysis paradigms, yet there is not a widely accepted metric for quantifying data quality.

In order to improve consistency, transparency and experimental repeatability, we propose a reporting a universal metric of ERP data quality that can be applied to virtually any kind of measurement of any ERP component in any experiment. Crucially, this allows comparison across subjects, in different experimental paradigms, and across different labs.

To do so, we need to specify such metrics. One possible metric to report is the parametric Standard Error of the Mean (SEM) of experimental targets. This has the advantage of clear interpretation, but cannot be calculated for many measurements, like the onset or peak latency of an ERP.

We show that, in both simulations and real data, Bootstrap Estimate of the Standard Error (BESE) is very close to SEM. BESE has the further advantages that it is robust to non-normal distributions and can be generated from observations for measurements in which pSEM cannot. We provide examples of using BESE to report noise in a simple EEG experiment, and example code to generate this.

We examine experimental data from a P3 design, where deliberate differences in recording set-up gives subtle differences in data quality. The resulting ERPs in the high- and low-noise conditions were broadly similar. With these BESE data quality metrics, we can identify and quantify the electrodes with higher noise, and do so in a way that does not corrupt later significance testing.

Disclosures: **A.X. Stewart:** None. **S.J. Luck:** None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.17/III59

Topic: I.07. Data Analysis and Statistics

Title: A method to estimate the active site by the brain functional connectivity networks based on electroencephalograms during various facial expressions

Authors: ***A. WATANABE**¹, T. YAMAZAKI¹, I. NEMOTO²

¹Kyushu Inst. of Technol., Izuka-Shi, Japan; ²Tokyo Denki Univ., Inzai-Shi, Japan

Abstract: Objective: To get an estimation of the activated brain areas, we propose a method to construct and quantify brain functional connectivity networks (BFCNs). These show which pairs of electrodes are highly synchronized, determined by synchronization likelihood (SL). SL calculated from electroencephalogram (EEG) is one of very useful indexes to reveal how the neurons in the brain are related or synchronized each other. The SL indicates how each pair of electrodes synchronize at some frequency bands, such as lower alpha (8-10 Hz), upper alpha (10-13 Hz) and beta (13-30 Hz). Moreover, SL could change in almost millisecond order. As EEGs have high time resolution, we constructed BFCNs based on the time course of SL. Then, we used

the BFCNs to get an estimation of the activated brain area. **Method:** Our subjects are all Japanese males and females, nineteen to twenty-six years old. We will gather the data from around twenty subjects in the further study. We applied the method we proposed to the EEGs measured during various facial expressions, such as smiling, anger and sadness. Then, we discuss the accuracy of the method by comparing the results with functional Magnetic Resonance Imaging (fMRI) data. **Results:** For now, there is a unique tendency in BFCN analysis in one frequency band(Fig.1). The graphs in Fig.1 show every BFCN during the facial express are plotted in the axis of those Rightness vs Frontness. fMRI measured during various facial expressions will be compared with the BFCN analysis. **Conclusions:** The activated area seems to follow the muscle movement. However, the right side of the brain were highly activated by smiling. As this stage, we can say facial expressions, especially smiling, have some effects on the right side of the brain.

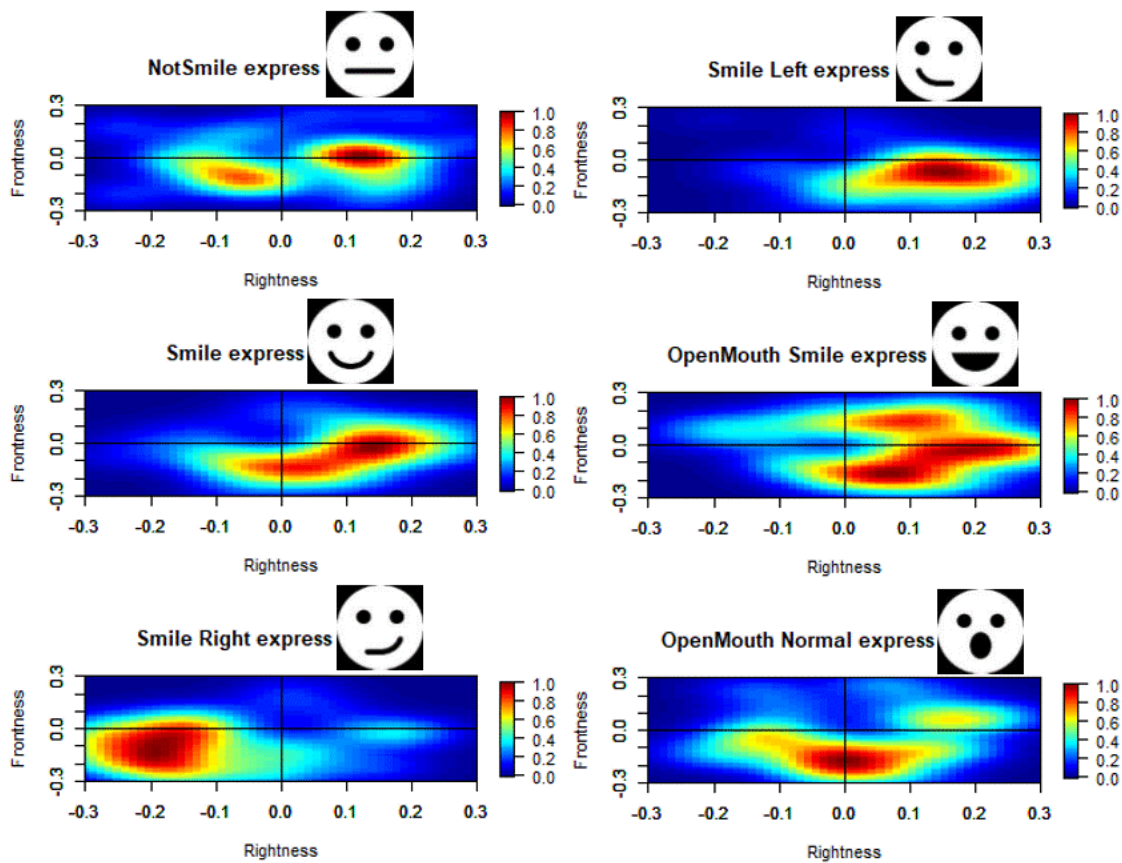


Fig.1 The estimated active site during various facial expressions

Disclosures: A. Watanabe: None. T. Yamazaki: None. I. Nemoto: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.18/III60

Topic: I.07. Data Analysis and Statistics

Support: NIH NS088590
NIH TR000448
NIH MH104592
the Jacobs Foundation
the Child Neurology Foundation
the McDonnell Center for Systems Neuroscience
the Mallinckrodt Institute of Radiology

Title: Three distinct sets of connector hubs integrate human brain function

Authors: *E. M. GORDON¹, C. J. LYNCH², C. GRATTON³, T. O. LAUMANN³, A. W. GILMORE⁴, D. J. GREENE⁵, M. ORTEGA³, A. L. NGUYEN³, B. L. SCHLAGGAR⁶, S. E. PETERSEN⁷, N. U. F. DOSENBAACH⁸, S. M. NELSON¹

¹Ctr. of Excellence for Res. on War Veterans, Waco, TX; ²Psychology, Georgetown Univ., Washington, DC; ³Neurol., Washington Univ. in St. Louis, Saint Louis, MO; ⁴Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD; ⁵Psychiatry, Washington Univ. Sch. of Med., Saint Louis, MO; ⁶Dept Neurol, Div. Child Neurol, Washington Univ, Sch. Med., Saint Louis, MO; ⁷Div. Neurol, Dept Neurol, Washington Univ. Sch. Med., Saint Louis, MO; ⁸Neurol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: The human brain is organized into discrete large-scale networks that enable distinct cognitive and behavioral processes. These include processing (i.e. sensory/motor) networks, networks representing memories and emotions (i.e. default network), and control networks. Complex behaviors, which often require top-down control over lower-level processes, are presumably enabled by interactions between these networks. Such network interactions, which can be described using resting-state functional connectivity (RSFC) fMRI techniques, are likely facilitated by specialized brain regions known as “connector hubs”. Previous work has treated connector hubs as a single category of brain object; however, this work was conducted in group-average data, which may confound observed network interactions. Here, we investigated the nature of connector hubs in individual humans using RSFC measures calculated from individual-specific regions in the highly-sampled individuals of the Midnight Scan Club (MSC) dataset, as well as in individuals from the Human Connectome Project (HCP) dataset. In individuals in both datasets, we observed that hub regions are separable into three distinct categories: 1) hubs that integrate control networks with processing networks; 2) hubs that integrate control networks with

the default network; and 3) hubs that integrate control networks with each other. The connective patterns and spatial distributions of these three hub categories replicated across datasets. Hubs of different categories were shown to occupy distinct positions within the brain's network structure. Further, network structures were affected in distinct and specific ways when hubs of each category were artificially "lesioned" (i.e. removed from the network). Finally, in both datasets, hubs in different categories demonstrated distinct patterns of activation across multiple different tasks, above and beyond differences driven by network identity. Together, this work suggests a model of brain organization in which different connector hubs integrate control functions and allow top-down regulation of separate processing streams, enabling control of discrete and separable cognitive functions.

Disclosures: E.M. Gordon: None. C.J. Lynch: None. C. Gratton: None. T.O. Laumann: None. A.W. Gilmore: None. D.J. Greene: None. M. Ortega: None. A.L. Nguyen: None. B.L. Schlaggar: None. S.E. Petersen: None. N.U.F. Dosenbach: None. S.M. Nelson: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.19/III61

Topic: I.07. Data Analysis and Statistics

Title: The convergence of quantitative EEG values over long sample times

Authors: *G. J. MAY¹, E. M. GORDON¹, L. ZAMBRANO-VAZQUEZ¹, H. WAHBEH², S. M. NELSON¹

¹Ctr. of Excellence for Res. on War Veterans, Waco, TX; ²Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Background: The collection of resting state EEG for quantitative analysis is a commonplace practice. Normative measures of power and coherence are often interpreted in the form of "Z-scores," defined as the number of standard deviations a given measure is from a population's mean value. Despite a number of publications on the reliability of qEEG values, relatively little has been said about the duration a sample needs to reach maximum reliability. To explore this question, we examined longer sessions of resting state EEG to determine whether the tradeoff between session duration and measure precision can be quantified. Method: N=45 Veterans age 25 to 65, with PCL scores ranging from 17 to 84 underwent 55 minutes of resting state EEG with eyes open, using a 32-channel Biosemi amplifier at 1024 Hz. EEG was downsampled to 128 Hz, with 0.2 Hz high pass filter applied. Power and coherence was computed at each timepoint. Resampling was done with increasing sample durations. Curve fitting was performed, and curves were used to estimate the time needed to reach a given precision for each EEG measure. Results: As expected, the disagreement between randomly

selected samples decreased as the size of the sample increased. Moreover the data conformed to a two-term exponential model, which allowed us to predict the speed of convergence for any given measure. By the time 30 minutes of data is collected, a majority of Z scores can be expected to be within 0.5 standard deviations of their “true” value. This drops as low as 10 minutes for a central and parietal power measures, and 60 minutes or higher for occipital power measures as well as most long-range beta coherence measures. Discussion: These data suggest that qEEG tends to reflect a stable underlying value that can be converged upon given enough data. If these values are stable from one day to the next, one might predict that reliability estimates could be increased using samples of a longer duration. The methods described here can be used in the evaluation of individual patients to estimate the precision of a qEEG measurement, and the amount of time needed to reach a desired level of precision. Confirmatory research will be required in the case of long estimated collection times, and the stability of these more precise measures from day to day.

Disclosures: G.J. May: None. E.M. Gordon: None. L. Zambrano-Vazquez: None. H. Wahbeh: None. S.M. Nelson: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.20/III62

Topic: I.07. Data Analysis and Statistics

Title: Regression analysis of the resting tremor local field potentials in Parkinson’s disease: Toward graded adaptive DBS control

Authors: *L. YAO, M. SHOARAN
Cornell Univ., Ithaca, NY

Abstract: Parkinson’s Disease (PD) patients treated by continuous Deep Brain Stimulation (DBS) exhibit side effects such as speech impairment and psychiatric symptoms. The adaptive DBS delivers the stimuli when needed by measurement of relevant biomarkers [1]. Most of the existing adaptive DBS systems, however, are based on on-and-off control, while the continuous and graded control is still lacking. We correlate the strength of the tremor symptoms with brain activity in subthalamic nucleus (STN), with the aim of providing adaptive DBS with graded control.

16 PD patients were recruited at the University of Oxford. The Local Field Potentials (LFPs) were recorded in the STN when stimulation was off, and the acceleration of the contralateral limb was simultaneously recorded. The acceleration signal was band-pass filtered at tremor frequency with a bandwidth of 2Hz, then the envelope was extracted using the Hilbert transform. The LFP data was segmented into 2-second epochs. Eight features were extracted from each

channel, including: 1. The individual tremor frequency band power; 2. Beta power (13-30Hz); 3. Low gamma power (31-45Hz); 4. The high frequency oscillation (HFO) power ratio between (200-300Hz) and (300-400Hz); 5. Hjorth activity, mobility and complexity; 6. Wavelet entropy. The extracted feature vector (8 features \times 7 channel = 56 features) was used to predict the measured tremor by using the stepwise linear regression.

Among 56 features, 8.6 ± 3.1 features were selected on average across 16 patients. The averaged R^2 coefficients were 0.61 ± 0.17 . The regression performance of two representative subjects are shown in Figure 1. This study offers the potential to improve the conventional on-and-off control of DBS using a new graded approach, where the DBS stimulation intensity could be continuously controlled by the predicted tremor strength from proposed regression analysis.

[1] A. C. Meidahl, G. Tinkhauser, D. M. Herz, H. Cagnan, J. Debarros, P. Brown, "Adaptive Deep Brain Stimulation for Movement Disorders: The Long Road to Clinical Therapy," *Mov. Disord.*, vol. 32, no. 6, pp. 810-819, 2017.

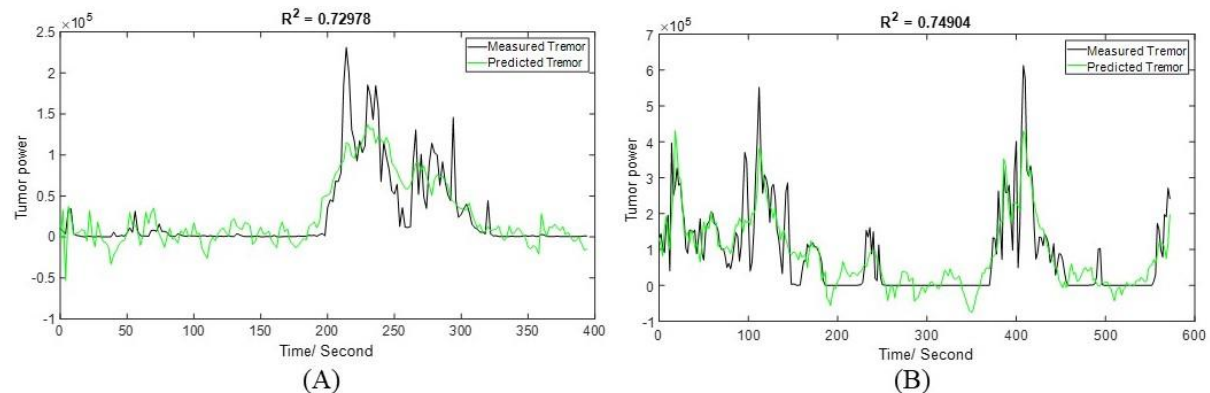


Figure 1. Regression analysis of the measured tremor and LFP features. Two representative subjects are separately shown in (A) and (B). Note: the black line indicates the measured tremor from acceleration recording, while the green line indicates the predicted tremor from LFP recording.

Disclosures: M. Shoaran: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.21/III63

Topic: I.06. Computation, Modeling, and Simulation

Support: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 785907

Title: The brain simulation platform of the human brain project - v2.0: Building brain models in a collaborative environment

Authors: *L. BOLOGNA¹, C. A. LUPASCU¹, R. MIGLIORE¹, J.-D. COURCOL², F. SCHUERMANN², A. P. DAVISON³, M. MIGLIORE¹

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Abstract: The Brain Simulation Platform (BSP) of the Human Brain Project (HBP) offers the scientific community a set of tools and services for the formalization, reconstruction, simulation and analysis of data-driven brain models. The Platform leverages the HBP Collaboratory's framework in order to allow the creation and organization of common workspaces (known as *Collabs*) where collaborators can share data, results, methods and algorithms. The new version is based on a modular design catering to a wide variety of uses. In particular, it now features mature functionality for the creation of single cell models, for *in silico* experimentation with single cells, scaffold microcircuit, brain region models, and a framework to validate models against a growing set of experimental data in an automated and repeatable manner. The seamless integration with the Neuroinformatics Platform, through the open source Blue Brain Nexus technology, and the tight integration with the HBP's High Performance Analytics and Computing Platform makes the BSP a unique tool in the field.

In this poster we present the most recent release of the platform which, among several new features, offers a number of ready-to-run applications and Jupyter notebooks for many modeling use cases and a catalog of downloadable models. An integrated usage monitor app collects real-time and past statistics of the operations performed on the BSP and on the type of users (e.g. new, returning, HBP internal/external) interacting with the environment. The results, some of which are shown in Fig. 1, demonstrate the expanding worldwide use of the platform to investigate a variety of scientific issues in the computational neuroscience field.

The BSP is available at this link: <https://collab.humanbrainproject.eu/#/collab/1655/nav/28538>
For more info and support please contact bsp-support@humanbrainproject.edu

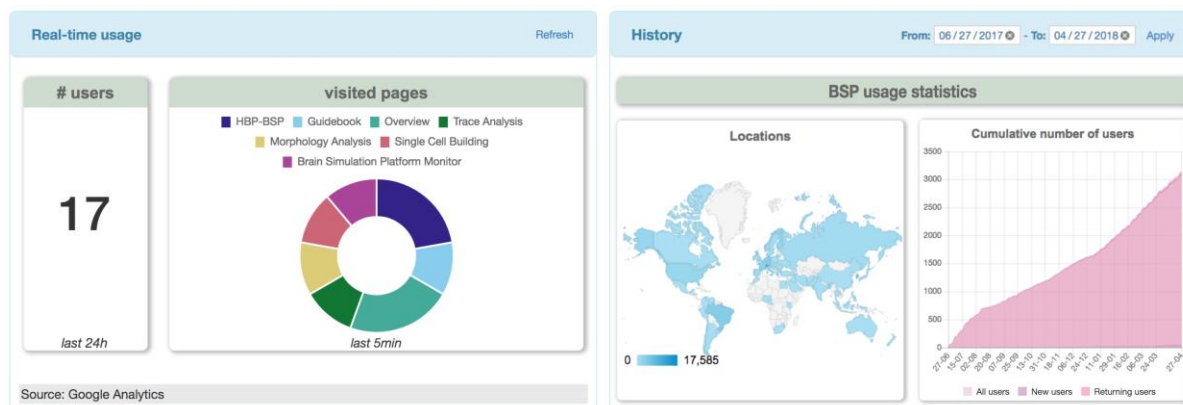


Fig. 1 Example of panels displayed in the BSP monitor

Disclosures: L. Bologna: None. C.A. Lupascu: None. R. Migliore: None. J. Courcol: None. F. Schuermann: None. A.P. Davison: None. M. Migliore: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.22/III64

Topic: I.07. Data Analysis and Statistics

Title: Investigating the role of fiber tractography in DBS target localization

Authors: V. K. SRIVASTAVA, *C. BOULAY, A. J. SACHS
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Abstract: Background: With the advent of diffusion magnetic resonance imaging (MRI) technology and analysis, recent work has evaluated the clinical utility of white matter tract imaging in the preoperative planning strategy to localize targets for deep brain stimulation (DBS) in patients with movement disorders. Objective: The overall aim is to retrospectively compare the current clinical standard with novel tractography-based methods for localizing DBS targets with respect to predicting clinically effective contacts for tremor alleviation. Rationale: This exploratory work has employed advanced diffusion modeling techniques to image white matter anatomy not currently utilized in clinical practice that will determine the location of relevant white matter tracts in relation to the implanted DBS electrodes. Results from this work will clarify the anatomical substrates responsible for the efficacy of DBS treatment that will aid in the preoperative planning for DBS surgery. Methods: A cohort of 4 patients with essential tremor were bilaterally implanted with DBS electrodes into the ventral intermediate (Vim) thalamic nucleus. The corticospinal tract (CST), medial lemniscus (ML), and dentatorubrothalamic (DRT) tract were tracked using a variety of diffusion models such as diffusion tensor imaging (DTI), generalized q-sample imaging (GQI) and constrained spherical deconvolution (CSD). The location of these tracts was analyzed in comparison to recent tractographic methodologies for Vim thalamic nucleus localization, and in relation to DBS leads that were segmented from postoperative CT scans. Results: This work has shown robust depiction of the CST, ML and DRT pathways using the CSD diffusion model. Furthermore, the DRT pathway was shown to traverse the delineated Vim nucleus in close proximity to DBS lead contacts. Conclusion: A novel workflow has been developed to assess the location of white matter tracts of interest in relation to delineated deep brain nuclei and implanted DBS electrode contacts, which will provide additional information to the neurosurgeon for stereotactic targeting of deep brain structures and to the clinician for determining the optimal postoperative programming stimulation parameters to control motor symptoms.

Disclosures: V.K. Srivastava: None. C. Boulay: None. A.J. Sachs: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.23/III65

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01-NS094206
NIH Grant R01-NS081118

Title: Comparison of algorithm complexity when programming DBS systems with multi-objective particle swarm optimization

Authors: *M. GOFTARI¹, E. PEÑA², S. ZHANG³, M. D. JOHNSON⁴

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Abstract: Recent advances in directional deep brain stimulation (DBS) lead technology have enabled more precise and selective modulation of neural pathways within the brain; however, with the increased number and distribution of electrode sites, efficiently identifying therapeutic stimulation settings can be a significant challenge within a clinical setting. Recent advancements in semi-automated computational algorithms for programming DBS systems, including those based on particle swarm optimization (PSO), hold promise in reducing the dimensionality and time of the programming process. In this study, we further developed a multi-objective PSO approach designed to identify DBS settings that more selectively targeted subthalamic nucleus (STN) efferents and hyperdirect pathway afferents over other axonal pathways implicated in side effects of STN-DBS, including direct activation of the corticospinal tract of internal capsule. Specifically, the algorithm included two new features: (1) integration of a modified driving function instead of an activating function to predict axonal membrane polarization resulting from DBS, and (2) widening the multi-channel independent current controlled amplitude constraints to allow for both monopolar and bipolar electrode configurations. The algorithm was evaluated in the context of a subject-specific computational model of STN-DBS in a parkinsonian non-human primate. Prediction of neuronal pathway activation within and adjacent to the STN aligned more accurately to multi-compartment biophysical neuron model simulations when the multi-objective PSO algorithm incorporated the modified driving function method in lieu of the activating function method. Additionally, the PSO algorithm most often predicted bipolar instead of monopolar DBS settings. Given the large stimulation parameter space available for directional DBS leads, computational algorithms as described here have significant potential to increase clinical efficiency and enhance the physiological interpretation of neuromodulation therapies.

Disclosures: M. Goftari: None. E. Peña: None. S. Zhang: None. M.D. Johnson: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.24/III66

Topic: I.07. Data Analysis and Statistics

Title: Qualitative research and user-centered design of deep brain stimulation

Authors: *Z. SUSKIN^{1,2,3}

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³Pellegrino Ctr. for Clin. Bioethics, Washington, DC

Abstract: *Background:* Deep Brain Stimulation (DBS), a neurosurgical procedure popularly used to treat movement disorders, has gained traction for wide therapeutic use worldwide. However, the technocratic development of DBS has lacked non-standardized, non-clinical, and non-quantitative outcome data. It is increasingly recognized that technical and ethical design and development of DBS should be informed by the ‘lived experiences’ of patients, families, caregivers, and healthcare professionals. Such open-ended, qualitative research may better inform user-centered design and subjective outcomes.

Objectives: This meta-analysis had two goals: determine the composition of qualitative research being collected on DBS; and ascertain the content of non-standardized, non-clinical, and non-quantitative perspectives of DBS.

Methods: A systematic search of PubMed Medline was conducted for qualitative data on DBS. Inclusion criteria comprising ‘target studies’ (TS) of ‘target participants’ (TP) were any study using non-standardized qualitative methods, assessing end-users’ ‘lived experiences,’ or including non-patient subjects. Composition was analyzed in five domains: year of publication, study location, patient diagnosis, and time(s) and method(s) of qualitative assessment. Content was analyzed thematically.

Results: An initial search returned 1,273 publications. 505 studies (S) of 22,452 participants (P) were relevant. Of these, 86 (17%) TS of 5,179 (23%) TP met inclusion criteria. *Publications by Year:* last 5 years (S: 43%, TS: 56%, P: 57%, TP: 74%), average change per year (S: +30%, TS: +7%, P: +103%, TP: +35%). *Location:* 36 countries - USA (S: 24%, TS: 23%), Europe (S: 54%, TS: 57%), other (S: 22%, TS: 20%). *Diagnosis:* 31 illnesses - Parkinson’s (S: 57%, TS: 73%), other movement disorders (S: 28%, TS: 16%), neuropsychiatric (S: 7%, TS: 8%), pain (S: 3%, TS: 0%). *Follow-up Time (months):* range (Pre-DBS - 199.2), average (S: 11.3, TS: 8.9), < 12 (S: 74%, TS: 64%), > 60 (S: 3%, TS: 2%). *Methods of Qualitative Assessment:* 1215 assessments administered, 215 distinct methods - standardized (91%), non-standardized (9%); patient (95%), caregiver (3%), healthcare professional (2%). Seven themes emerged from the content of TS: global perspectives, personhood, social interactions, procedural experiences, device effects, caregiver burden, and healthcare professional evaluation.

Conclusions: The composition of qualitative data collected on DBS had mixed results. Investigation is still underway regarding a satisfactory threshold of types of qualitative studies and the degree to which DBS designers incorporate such data and/or perform research.

Disclosures: Z. Suskin: None.

Poster

090. Data Analysis and Statistics: Human Data: EEG, Electrophysiology, and DBS

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 090.25/III67

Topic: I.06. Computation, Modeling, and Simulation

Title: Computational modeling for personalized and optimized deep and targeted temporal interference brain stimulation

Authors: A. M. N. CASSARA¹, *E. NEUFELD², E. S. BOYDEN³, N. KUSTER⁴, N. GROSSMAN⁵

¹IT'IS Fndn., Zurich, Switzerland; ²Computat. Life Sci., IT'IS Fndn., Zuerich, Switzerland; ³MIT, Cambridge, MA; ⁴ETH Zurich & IT'IS Fndn., Zurich, Switzerland; ⁵Ctr. for Bioinspired Technol., Imperial Col. London, London, United Kingdom

Abstract: Temporal interference (TI) stimulation [Grossman, Cell, 2017] is a form of brain stimulation where two or more high frequency currents (typically 1-4 kHz) with slightly differing frequencies are applied, resulting in a targeted neurostimulation at the difference frequency in locations where the envelope modulation that results from the superposition of the fields is sufficiently large. It was shown in live mouse brain, that TI stimulation can be used to recruit neural activity in deep brain structures, e.g., the hippocampus, without activation of overlaying cortex. However, the highly inhomogeneous nature of the head makes selective stimulation difficult. To support the use of TI stimulation in humans, we developed a computation framework to perform personalized modeling and optimization (targeting, side-effect minimization) of TI stimulation in humans. The treatment modeling/ optimization was implemented within the Sim4Life computational life sciences platform and consists of the following steps: 1) personalized anatomical model generation using *de novo* image segmentation of image-based morphing of high resolution detailed computational head models; 2) placement of candidate electrodes using a 10-/20-system or interactive positioning; 3) discretization, tissue property assignment, and quasi-electrostatic electro-magnetic (EM) modeling to determine the induced fields from electrode pairs; 4) analytical computation of TI modulation amplitude distributions at either a predefined orientation (e.g., radial to the tissue surface, corresponding to the main neural axis) or at an orientation with maximal envelope modulation amplitude; 5) evaluation of stimulation selectivity, i.e., percentage of activated target region vs. percentage of non-target activation, based on the cumulative histogram of the envelope modulation amplitude;

6) constrained optimization using SciPy's COBYLA algorithm; and 7) modeling of coupled EM-neuron dynamics using anatomically positioned morphologically and electrophysiologically detailed neuron models. The computational modeling was used to investigate the feasibility of targeting the TI stimulation to a selective number of brain regions with high clinical relevance, such as the hippocampus, the amygdala, and the insula. Even without optimizing electrode size and their detailed placement, selectivity in the order of 84% target activation at 6% non-target activation (competing goals) could be achieved using unexpected montages of two electrode pairs. Next steps will involve multi-goal optimization, uncertainty assessment, experimental validation, and further mechanistic investigations.

Disclosures: **A.M.N. Cassara:** A. Employment/Salary (full or part-time);; IT'IS Foundation. **E. Neufeld:** A. Employment/Salary (full or part-time);; IT'IS Foundation, ZMT Zurich MedTech AG. 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.; SPARC Initiative (NIH), RESTORE project (EUROSTARS), NEUROMAN (CTI). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Minority Shareholder ZMT. **E.S. Boyden:** None. **N. Kuster:** A. Employment/Salary (full or part-time);; IT'IS Foundation, ZMT Zurich MedTech AG, SPEAG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shareholder NFT, ZMT, SPEAG. **N. Grossman:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.01/III68

Topic: I.07. Data Analysis and Statistics

Support: ONR N00014-18-1-2069

Title: Quadratic discriminant analysis reveals representational dissimilarities between different types of auditory selective attention

Authors: *W. AN, A. PEI, B. SHINN-CUNNINGHAM
Biomed. Engin., Boston Univ., Boston, MA

Abstract: Introduction

Representational similarity analysis (RSA) has been proven successful in integrating MEG with fMRI data through the use of a representational dissimilarity matrix (RDM). Previous studies used support vector machine (SVM) to build MEG RDMs that could effectively differentiate conditions of different categories. How to build optimal RDMs for EEG studies, however, is yet

to be explored. This study examined the viability of using quadratic discriminant analysis (QDA) to improve the decoding accuracy in an EEG RDM for a study of auditory selective attention.

Method

12 adults participated in this study. The auditory stimuli were syllables Ba/Da/Ga spoken by 5 distinguishable talkers, each played from one of 5 possible directions (left/right 90°/30°, center). The experiment consisted of 21 conditions (36 trials each). Trials differed in the type of attention being tested (spatial/talker/no attention) and the gender/direction of the target. For each trial, the subjects were given a visual cue, an auditory cue (cueing period), and a 1-second gap (preparatory period) before the onset of a 4-syllable mixture. The cues conveyed information about the type of attention to be tested, and the direction/talker of the target. For a spatial- or a talker-attention trial, the subjects were asked to report the syllable from the target direction/talker in the upcoming mixture. In control trials, subjects were asked to respond with a random button press, ignoring the stimuli. 64-channel EEG, recorded throughout the experiment, was pre-processed using a customized script. Each time point in the EEG data during the cueing and the preparatory period were used to train and test SVM/QDA for neural decoding. Results of SVM and QDA classifiers were compared in terms of the decoding accuracy during the two periods, i.e. the difference in evoked and induced responses, respectively. Student t-test was used for statistics.

Results

Both classifiers could decode Spatial vs Control (SpaCtr), Talker vs Control (TlkCtr) and Spatial vs Talker (SpaTlk) better than chance ($p < 0.01$) in both periods. QDA yielded higher decoding accuracy than SVM for the cueing period in SpaCtr ($57.91\% \pm 1.14\%$ vs $55.36\% \pm 0.76\%$, $p < 0.001$), TlkCtr ($57.45\% \pm 1.47\%$ vs $56.34\% \pm 1.23\%$, $p = 0.027$), and SpaTlk ($58.06\% \pm 1.07\%$ vs $55.47\% \pm 0.65\%$, $p < 0.001$). In the preparatory period, QDA outperformed SVM in SpaCtr ($52.48\% \pm 1.04\%$ vs $50.62\% \pm 0.65\%$, $p < 0.001$), TlkCtr ($51.78\% \pm 0.49\%$ vs $50.76\% \pm 0.50\%$, $p < 0.001$), and SpaTlk ($51.97\% \pm 0.77\%$ vs $50.51\% \pm 0.45\%$, $p < 0.001$).

Conclusion

QDA could reveal representational dissimilarities more effectively than SVM in EEG data, especially for induced responses.

Disclosures: W. An: None. A. Pei: None. B. Shinn-Cunningham: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.02/JJJ1

Topic: I.07. Data Analysis and Statistics

Support: CONACYT Grant 258942

Title: Visualization of changes in the dynamics of human gait using nonlinear time series analysis

Authors: *M. A. LANDA-JIMENEZ¹, F. M. MONTES-GONZALEZ¹, C. MORGADO-VALLE², L. BELTRAN-PARRAZAL², C. ISLAS-MORENO³, B. A. ITZA-ORTIZ⁴, F. MENENDEZ-CONDE⁴, R. LEONEL-GÓMEZ⁴, M. TETLALMATZI-MONTIEL⁴, J. VIVEROS-ROGEL⁴, E. E. RODRIGUEZ-TORRES⁴

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Abstract: The human gait is the process by which humans move from one place to another. Despite the individual nature of the process, similarities between subjects are such that a pattern of normal human gait can be observed. However, this pattern can change as consequence of extrinsic factors such as ground slope, shoes, etc., or physiological factors like bone alterations or diseases. In this work, we explore the use of nonlinear time series analysis in order to visualize changes on human gait using data collected through wearable inertial sensors. To observe the changes, we use a method known as *uniform reconstructed state space*, which allows us to reconstruct the dynamics of an unknown system using one dimensional time series. Specifically, we use the reconstructed state space to visualize changes within the human gait for 10 participants performing gait activity. This kind of visualization could be useful to develop better diagnostic tools for gait pathologies.

Disclosures: M.A. Landa-Jimenez: None. F.M. Montes-Gonzalez: None. C. Morgado-Valle: None. L. Beltran-Parrazal: None. C. Islas-Moreno: None. B.A. Itza-Ortiz: None. F. Menendez-Conde: None. R. Leonel-Gómez: None. M. Tetlalmatzi-Montiel: None. J. Viveros-Rogel: None. E.E. Rodriguez-Torres: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.03/JJJ2

Topic: I.07. Data Analysis and Statistics

Title: A real-time processing technique for 40 Hz auditory steady-state response: Exploratory application in cerebellopontine angle surgery

Authors: *S.-I. HIRANO, Y. NISHIKAWA
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Abstract: Brain surgery sometimes involves a risk of causing nervous system dysfunction due to surgical intervention. In cerebellopontine angle (CPA) surgery, in particular, neurosurgeons have been struggling to avoid this because there are many important neural structures, such as the brainstem and cranial nerves. Last year, we presented a real-time processing technique for the 40 Hz auditory steady-state response (40Hz-ASR). Today, we will show the potential of this technique to utilize as an intraoperative monitoring method in practical CPA surgery. Eight patients with vestibular schwannoma underwent CPA surgery. During the intervention, the 40Hz-ASR was continuously recorded, along with a conventional auditory brainstem response (ABR). Ag/AgCl dish electrodes had been placed preoperatively at the vertex and bilateral pinnae. Auditory clicks were presented successively at 40 Hz. The signals of the 40Hz-ASR were immediately digitized and analyzed by the Fast Fourier Transformation (FFT) method. The spectral power (SP) and the phase coherence measure (PCM) were calculated simultaneously. The pre-fixed real-time processing parameters for the 40Hz-ASR, which was detailed our previous study, were employed. A set of 65536 sweeps was sampled and processed by FFT. To achieve rapid data collection, each subset of 4096 data was forced to expire in a continuous first-in first-out fashion. Stability of the response was evaluated by PCM. PCM and SP were recorded on an HDD and displayed on a LCD monitor successively. The PCM increased and remained high after general anesthesia. In contrast, the SP declined constantly. Craniectomy and epidural manipulation had no effect on PCM and SP. However, the intradural CPA maneuver caused a change to them. Although a direct intervention to the acoustic nerve significantly worsened the PCM, the change was transient and reversible. Severe damage of the acoustic nerve and surrounding structures caused the waveform to disappear and the PCM to diminish irreversibly. The boundary level that predict postoperative hearing preservation was $0.7 > \text{PCM}$ after tumor removal although the PCM was below that level during invasive CPA manipulation. The usefulness and properties of the 40Hz-ASR as an intraoperative acoustic monitoring tool was confirmed. The combined use of PCM and SP could provide a rapid functional alert with sufficient accuracy and rapidity to preserve the cochlear and brainstem function. Our results suggest that on-line measurement of the PCM and SP may be applicable in intraoperative monitoring. We have obtained approval from the Institutional Clinical Research Committee prior to undertake this study, and has no COI to declare.

Disclosures: Y. Nishikawa: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.04/JJJ3

Topic: I.07. Data Analysis and Statistics

Support: NSERC Discovery Grant RGPIN-2015-06696
CFI PN 32896
Sony Faculty Research Award
SSHRC Insight Development Grant 430-2017-01189

Title: Population receptive field mapping of high-level visual cortex at 7 Tesla

Authors: *C. DAMIANO, C. LEFERINK, D. B. WALTHER
Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Decades of research have confirmed that all stages of processing within the visual system show retinotopic organization, from retinal ganglion cells to high-level visual areas, such as the parahippocampal place area (PPA). The parahippocampal cortex in particular has been shown to exhibit a peripheral field bias, which is commonly interpreted as leading to a lack of sensitivity to high spatial frequencies (Arcaro *et al.*, 2009). However, neuroimaging studies have shown that the PPA is activated more strongly by high than low spatial frequencies (Rajimehr *et al.*, 2011) and that scene content in the PPA is more efficiently conveyed by high than low spatial frequencies (Berman *et al.* 2017). Additionally, line drawings, which carry only high spatial frequency information, suffice to form scene category representations in the PPA (Walther *et al.*, 2011). How can this be the case if the PPA is not sensitive to high spatial frequencies? One drawback of the original retinotopic mapping of the parahippocampal cortex was the use of a checkerboard stimulus, to which higher-level visual areas are not particularly responsive. Thus, using a stimulus that is known to activate high-level visual cortex (images of objects of various sizes), we sought to thoroughly map out the population receptive fields (pRFs) in order to verify previous findings and explore the apparent contradiction regarding the representation of high spatial frequencies in the PPA. Here, we used the pRF scans from a subset of the participants in the Human Connectome Project database, obtained with high field strength (7T) fMRI, to quantify the pRF properties of high-level visual areas, such as the PPA. We estimated the eccentricity, polar angle, and size of the receptive fields using a nonlinear optimization model fitting procedure (Kay *et al.*, 2013). We then examined each voxel's receptive field size and eccentricity within the visual field. Within the PPA, we find a large number of voxels with RFs centered near the fovea (< 1 degree of visual angle), and a slightly smaller number of voxels with RFs centered in the mid-range to large-eccentricity regions of the visual field. Thus the peripheral field bias found previously seems not to hold when mapping pRFs with stimuli designed to activate high-level visual areas. Similarly, we found many voxels to have fairly small (< 0.5 degree radius) receptive fields, with both large *and* small receptive fields present near the fovea. In their combination, these results suggest that the PPA is sensitive to both low and high spatial frequency information. Our work highlights the importance of mapping high-level visual areas using stimuli that allow for sufficient activation of such areas.

Disclosures: C. Damiano: None. C. Leferink: None. D.B. Walther: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.05/JJJ4

Topic: I.07. Data Analysis and Statistics

Support: NIH/NIDCD R01 DC006287
Advancing a Healthier Wisconsin (CTSI)

Title: Nonlinear coupling of electroencephalography and functional magnetic resonance imaging responses to auditory syllables

Authors: *N. J. HEUGEL¹, E. LIEBENTHAL³, S. A. BEARDSLEY²

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Abstract: The growth in using noninvasive multi-modal functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to characterize perceptual and cognitive processes in the human brain with high spatiotemporal resolution has made understanding the relationship between the modalities a priority. We quantify the relationship between blood-oxygen-level-dependent (BOLD) fMRI and mass neural activity measured by event-related potentials (ERPs) in response to syllables delivered at varying rates, to assess the normative dependence of fMRI-EEG coupling on stimulus rate.

Simultaneous fMRI and EEG was collected in 13 subjects, while performing a target detection task with 4 second trains comprised of 7 different auditory syllables (each 200 ms long), presented at varying rates (0.25, 0.5, 0.75, 1, 1.5, 2, 2.5 and 3 Hz). The group average response for each rate was calculated and then entered into a joint independent component analysis (jICA) using a within subject across levels data structure. The threshold for EEG and fMRI was defined as the 95% amplitude value relative to all components. Two components with fMRI and EEG measurements exceeding this threshold were selected for further analysis. ROIs were defined based on the fMRI activity, and used to calculate weighted mixing coefficients for each modality (1).

The stimulus-rate dependent EEG and fMRI activity was parsed into two components. Spatially, the activity in both components largely overlapped in the bilateral superior temporal gyrus, but extended to the left parietal operculum for component 1, and to the left supramarginal gyrus for component 2. Temporally, the activity in component 1 peaked within the first 1.5 seconds from syllable-train onset, whereas that in component 2 was distributed over the duration of the train. The weighted mixing coefficients of component 1 increased roughly linearly with syllable presentation rate, whereas the coefficients of component 2 peaked at low presentation rates (0.75 Hz), and decreased at higher rates.

Component 1 may capture the activity of slow auditory neurons that responded only to the train onset. Component 2 may capture the activity of faster auditory neurons that tracked each syllable onset. The latter neurons have a brief response, and may contribute more to EEG than fMRI measurements, resulting in nonlinear coupling between the modalities at low presentation rates (when syllables within the train are discrete). Thus, different fMRI and EEG joint components may reflect the activity of neuronal assemblies with different temporal profiles and function.

1. Mangalathu-Arumana et al., *Frontiers in Neuroscience*, 2018. Vol. 12.

Disclosures: N.J. Heugel: None. E. Liebenthal: None. S.A. Beardsley: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.06/JJ5

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF1566621

NSF1439221

NIH EY014800

Title: Inferring saccadic modulation sources and their computations using a model-based characterization of spiking responses in extrastriate visual cortex

Authors: *A. AKBARIAN AGHDAM¹, K. NIKNAM¹, B. NOUDOOST², N. NATEGH^{1,2}

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Abstract: We move our eyes about three times a second to bring the objects of interest to the fovea for further processing of the visual information. These rapid eye movements, called saccades, cause various changes in the neural responses and in our perception of the the visual world. Neurons in the visual areas modulate their responses based on a combination of the visual information available from the presaccadic scene, the postsaccadic scene, and the saccade target. The degree to which these various sources of modulation alter neuronal responses during the eye movements and their timecourse is not well understood. We have designed a high spatiotemporal resolution paradigm for measuring visual responses across eye movements, and developed a statistical framework to quantitatively describe neuronal responses recorded during the task. The model extends the generalized linear model (GLM) framework to account for the neurons' time-varying spatiotemporal sensitivity associated with the dynamic brain states induced by the eye movement. This state-dependent framework-termed the state-variable generalized linear model (SVGLM), with its parameters fitted directly to the spiking responses of the neurons in the middle temporal cortex (MT) of monkeys, can account for the modulations of perisaccadic

responses on the fast timescale of a saccade. We use this model to dissociate multiple sources of response modulations, and quantify their dynamics by characterizing their effects on the instantaneous response generation across a saccade. These analyses enable us to elucidate the underlying modulatory computations in terms of source-specific additive or gain factors and as a function of the brain state varying with an eye movement.

Disclosures: **A. Akbarian Aghdam:** None. **K. Niknam:** None. **B. Noudoost:** None. **N. Nategh:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.07/JJJ6

Topic: I.06. Computation, Modeling, and Simulation

Support: CIHR
NSERC

Title: A standardization of the visual contrast response function

Authors: ***M. DEMERS**¹, N. CORTES², V. ADY³, C. F. CASANOVA⁴

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Abstract: All neurons of the visual system exhibit changes in their firing rate as a response to differences in luminance. This neural response to visual contrast, also known as the contrast response function (CRF), follows a characteristic sigmoid shape that can be fitted with the Naka-Rushton equation (NRE). Four parameters define the CRF, which are used in different visual research disciplines to describe particular variations of neural responses. As novel technologies have grown, the capacity to record thousands of neurons simultaneously brings new challenges: processing and robustly analyzing larger amounts of data to maximize the outcomes of experimental measurements. Nevertheless, current guidelines to fit neural activity based on the NRE have been poorly discussed in depth. For this purpose, we have created a simplified theoretical model of spike-response dynamics, in which a homogeneous Poisson process generates the firing rate of neurons. To estimate the error of our model, the CRF obtained from these simulations, the empirical curve, is compared with the curve that generated these data points, the theoretical curve. First, a condition to determine the neuronal response saturation is proposed, indicating the possibility of scalability of the luminance in the experiment. Then, different CRF metrics in a single (SU) and multi-unit (MU) signals are analyzed. The results reveal that is always advantageous to either identify SU or assume MU formed of several SU

when calculating the CRF. Furthermore, a robust analysis of the sensibility of all parameters for the fit of the NRE is provided. Afterward, various least-square curve-fitting boundaries are tested to rank them according to their errors. It was observed that either removing or imposing loose boundaries to the CRF parameters lead to an increase of the error. Our findings indicate that there is an optimal range that allows for 1) maximize the fit of each parameter, and 2) minimize the number and time of stimuli required to achieve this goal. Finally, the optimal theoretical results were successfully tested on the cat's visual cortex. Thus, the designed tool allows an optimal design of stimuli to assess the CRF of large neuronal populations, providing the finest fit for each unit analyzed.

Disclosures: M. Demers: None. N. Cortes: None. V. Ady: None. C.F. Casanova: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

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Program #/Poster #: 091.08/JJJ7

Topic: I.06. Computation, Modeling, and Simulation

Support: B.Travers NARSAD Young Investigator Award from the Brain & Behavior Research Foundation
B. Travers UW Madison Startup funds

Title: Topological methods for modeling massive data in computational neuroscience and applications to networks in brain imaging, information in eye movement, communication of perceptual information in natural images, elucidation of features in neurodevelopment disorders, and attention: Local-to-global integration of information in nonlinear dynamical systems and spatiotemporal heterogeneous data

Authors: *A. H. ASSADI¹, A. ARDALAN², H. GAO⁷, M. NELSON³, E. QASEMI⁴, Y. SONG⁸, X. WANG⁵, J. XUAN⁹, E. DE LESTRANGE-ANGINIEUR¹⁰, B. TRAVERS⁶
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Abstract: Objectives

- (1) Establish topological methods and tools to unify development of data driven models for sensory-perceptual-cognitive processes;
- (2) Adapt advanced topological methods to organize information from given observations.

Significance: Neural data have multiple scales & resolutions. Data is diverse: numerical, imaging etc. Data processing, analytics and modeling provide a wealth of algorithms, techniques

and quantitative methods. Topological thinking allows unifying diversity of approaches through principles/reasoning suitable for heterogeneous multi-scale multi-resolution data that represent spatiotemporal variation, dynamical systems and communication of information.

Methods: Empirical topology is a general theory to transform (heterogeneous, multi-scale, multi-resolution) data into a space endowed with additional mathematical structure. Sample data from multiple experiments are used to estimate/learn the moduli space that represents phenotypic variation. Visual categorization model by Poggio et al and Empirical Topology (Assadi et al) are adapted to construct an empirical visual space (EVS). Neuronal response data are used to reconstruct dynamical systems (DS) in EVS at three sensory, perceptual, cognitive levels. EVS & DS conform with experimental results in vision psychophysics and neuronal processing pathways. The reconstructed DS are suitable for Deep Learning and enhance further modeling paradigms.

Results: (1) Deep Learning for prediction of Autism Spectrum Disorder (ASD) from subjects movements; (2) Analysis of eye movements for modeling visual memorability, attention and recall for image categories in architecture; (3) Quantifying phenotypic variation in dynamics of brain networks in health and disease; (4) Visual categorization and perceptual abstraction in Baroque paintings versus pre-Baroque and post-Baroque paintings; (5) Pattern recognition in complex neuronal dynamics through topological feature extraction; (6) Psychophysics and attention.

Conclusion: (1) Topological thinking inspires new hypotheses for association of phenotypic variation classes in dynamic brain networks to the corresponding behavioral observations, potentially useful for clinical diagnosis of ASD; (2) visual categorization and perceptual abstraction from paintings could be quantified, and agrees with text analysis from art history; (3) eye movement data from subjects agrees with human subject response in visual memorability, attention and recall for image categories in interior space architecture.

Disclosures: **A.H. Assadi:** Other; Senior Author. **A. Ardalan:** None. **H. Gao:** None. **M. Nelson:** None. **E. Qasemi:** None. **Y. Song:** None. **X. Wang:** None. **J. Xuan:** None. **E. De Lestrage-Anginieur:** None. **B. Travers:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.09/JJJ8

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF 1566621
NIH EY014800
NSF 1439221

Title: A state-based statistical model for characterizing the modulation of sensory cortical responses

Authors: *K. NIKNAM¹, A. AKBARIAN AGHDAM¹, B. NOUDOOST², N. NATEGH^{1,2}

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Abstract: Modulation of neuronal responses to sensory information by various factors such as context or behavior plays a key role in how we perceive the external world. These modulatory factors result in a time-varying relationship between stimulus and responses, controlled by other non-stimulus factors. The main difficulty in studying this type of modulatory processing arises from the nonlinearity and nonstationarity in the computations underlying this variable stimulus-response relationship. Computational models are intended to provide a quantitative description of stimulus-response relationship; however, the existing solutions for handling the nonstationarity of response characteristics (such as window-based methods, adaptive filtering, or dynamical systems approaches) fail in capturing fast modulations or characterizing the possible sources of these modulations. We present a statistical model in the generalized linear model framework, termed as the state-variable generalized linear model (SVGLM), which is capable of accounting for the dynamics of neural responses on fast timescales. Further, by factorizing the SVGLM, in a statistically optimal sense, into its multiple modulatory components, we are able to characterize the independent contributions of multiple response sources associated with those modulations. The resulting factorized SVGLM (F-SVGLM) is tested for its ability to predict the time-varying response of the neurons in the middle temporal (MT) cortex of macaque monkeys during an eye movement task. The model, with its biophysically interpretable components, accurately predicts neuronal responses on the timescale of a rapid eye movement (saccade). Moreover, the model is able to dissociate the contribution of each participating modulation sources and quantify their time course and magnitude in generating the instantaneous response of MT neurons at the level of single spike trains. By providing a statistical description of the spiking data, the model serves as a powerful tool to investigate how an MT neuron's spatiotemporal sensitivity changes during a saccade, allowing us to study the neuronal basis of perisaccadic changes in the perception of time and space.

Disclosures: K. Niknam: None. A. Akbarian Aghdam: None. B. Noudoost: None. N. Nategh: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.10/JJ9

Topic: I.06. Computation, Modeling, and Simulation

Support: NIDCD DC014279

Title: Speaker-independent auditory attention decoding without access to clean sources

Authors: *Y. LUO¹, J. O'SULLIVAN¹, J. L. HERRERO², A. D. MEHTA^{3,2}, N. MESGARANI¹

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Abstract: In a natural auditory environment, most people can easily attend to a particular speaker out of many. However, this task remains challenging for those suffering from hearing impairments. Current hearing aids don't help because they don't know who a user is paying attention to, so they can't suppress competing talkers. Cognitively controlled hearing aids that can automatically identify and amplify an attended speaker are the next step in offering help. One of the major challenges in achieving this goal is separating the multiple acoustic sources in the environment. Recent work has shown that deep neural networks (DNNs) can be trained to isolate specific speakers that a user may frequently interact with. However, such a system will not work when a listener attends to new, unseen speakers in the environment. Another limiting factor in current speech separation algorithms is their intolerably long latency which is due to the use of a high-resolution short-time Fourier transform (STFT) as a feature extraction step. Here we address these challenges by incorporating a recently proposed time-domain, real-time, speaker-independent, single-channel speech separation algorithm into the auditory attention decoding platform. We tested our system using neural data obtained from patients undergoing invasive neural recordings for treatment of epilepsy. They were presented with mixtures of 2 speakers, and were asked frequently to alternate their attention between the two. Using our recently proposed Time-domain Audio Separation Network (TasNet), we could successfully separate the unseen speakers from the mixture. The separated speech signals and the neural responses are then mapped to a common low-dimensional subspace, in which the attended speaker is decoded by calculating the similarity between the neural responses and the separated speech stimuli. We show that the proposed algorithm can potentially be implemented in real-time with a latency as low as 10 ms and can help a hearing impaired user to attend and communicate with unseen speakers by eliminating the need for retraining the speech separation module.

Disclosures: Y. Luo: None. J. O'Sullivan: None. J.L. Herrero: None. A.D. Mehta: None. N. Mesgarani: None.

Poster

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.11/JJJ10

Topic: I.06. Computation, Modeling, and Simulation

Title: 3D simulation of the structural and functional properties of the human sensory system: Auditory and visual system

Authors: *M. EVREN^{1,3}, V. EVREN², E. O. KOYLU⁴

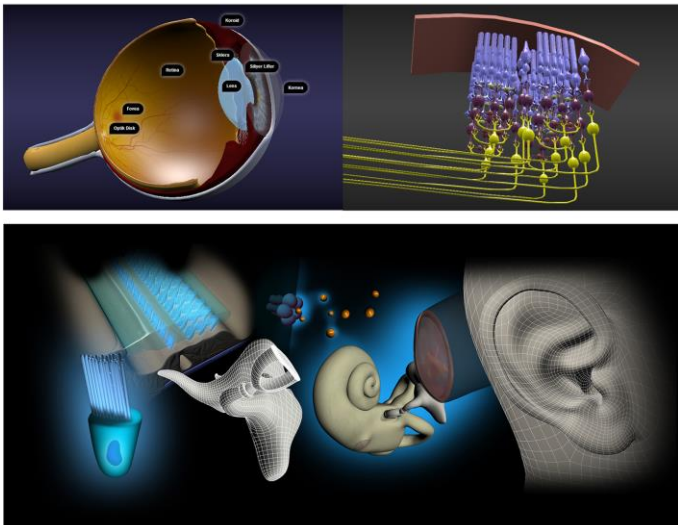
¹Biotech., Ege Univ., IZMIR, Turkey; ²Ege Univ., Izmir, Turkey; ³Biotech., natural and applied sciences, Izmir, Turkey; ⁴Ege Univ. Sch. Med., Izmir, Turkey

Abstract: Abstract:

OBJECTIVES: Use of three-dimensional applications in education and research has substantially increased in the past decade. Three-dimensional models are, now, preferred over two-dimensional illustrations in various life sciences such as medicine and biology. Sensory systems are among the most complex topics in neuroscience education in terms of explanation and representation of the functional mechanisms. Accurate modeling of related anatomical parts and simulation of mechanisms of the sensory systems in humans can provide an superior insight and contribution to the neuroscience education.

Auditory system and visual system has been selected in our study.

MATERIALS & METHOD: We prepared our digital assets as the first step in our project. In addition to existing visual materials in the textbooks, X-Rays, CT and MRI images were used in comparison for creating accurate 3D computer models. Measures and aspect ratios of the structures were preserved. By using the appropriate software and hardware, the functional properties and the effects of the sound waves on the structures of external, middle and internal ear and finally the conversion of these waves into neural signals have been modeled and simulated. For the eye physiology, by using the same methods, we have modeled the eye ball, the ocular layers, and the photoreceptor cells. Three dimensional modeling and graphical simulation of these sensory system comprised both microscopic and macroscopic mechanisms in order to achieve our goal. Modelings and all 3D animations/simulations were performed by using Autodesk Maya and Pixologic ZBrush.



Disclosures: M. Evren: None. V. Evren: None. E.O. Koylu: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.12/JJJ11

Topic: I.06. Computation, Modeling, and Simulation

Title: Development of Japanese eye typing system

Authors: *I. MOTOYAMA^{1,2}, T. UDA², M. YAMAZAKI³, N. OKAMOTO⁴, Y. KURODA⁵, H. EDA^{1,6}

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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. The virtual keyboard specialized in Japanese is still under research. We have developed a Japanese eye typing system. The purpose of this research is to examine the accuracy and facilities of the system.

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 four words with each of the four conditions (Fix+sub, Fix+others, Move+sub, Move+others). After the each session, the subjective difficulty was reported by Visual Analog Scale (VAS). The eye typing duration and the number of misinput were measured. The achievement ratio was also calculated.

We measured salivary amylase before and after the session and galvanic skin response (GSR) from the palm. The consent form was obtained from eight subjects. Experiment ethics and private information protection were fully considered.

Results

In both of the MoveVKB condition, the duration were significantly shorter than the FixVKB (Fix+sub: 74.1, Fix+other: 93.0, Move+sub: 52.5, Move+others: 62.7 Sec.). The number of misinput was small and the achievement ratio was higher in MoveVKB conditions compared to the FixVKB. VAS showed more difficulty in FixVKB. GSR showed more activated response at the time of misinput and no specific relation to the way of eye typings. OthresRef session showed obvious the deterioration in performance.

Discussion

MoveVKB enables eye typing more correctly than FixVKB. Although MoveVKB was assumed to reduce the stress using the eye tracking by othresRef, the salivary amylase value did not support it, because the individual difference was large. Evaluation of an eye tracking system is possible by the performance data, the number of mistakes, etc. The further discussion is expected with brain measurement data, as a next step.

Disclosures: **I. Motoyama:** None. **T. Uda:** None. **M. Yamazaki:** None. **N. Okamoto:** None. **Y. Kuroda:** None. **H. Eda:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

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Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.13/JJJ12

Topic: I.06. Computation, Modeling, and Simulation

Title: Development of mutual learning system for advanced educational research. - NIRS and GSR measurement during tangram puzzle -

Authors: ***M. YAMAZAKI**¹, **N. OKAMOTO**², **Y. KURODA**³, **H. EDA**⁴

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Abstract: Introduction

“Learning from the other” is one of learning styles in education, however its effectiveness has been unclear. If teachers can evaluate these effectiveness objectively, they will give students the appropriate way of teaching.

Near infrared spectroscopy (NIRS) calculates hemoglobin parameters, such as changes in oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb). We showed a study which speculated student’s motivation by measuring brain activities with NIRS (Yamazaki et al.,SfN2017).

This study was conducted to develop an evaluation tool which measures the biological reaction during the collaborate task to evaluate the subject’s performance objectively.

Method

1) Task

A total of 12 subjects were participated in this study. The consent form was obtained from all subjects. Experiment ethics and private information protection were fully considered.

We selected four tangram tasks and assigned them from easy to difficulty levels. The tangram is a Chinese puzzle consisting of seven flat shapes. A pair of two subjects sat next to each other as they could see each other, but they were forbidden in speaking. They were required to complete

the tangram tasks collaborated with the other and switched its role “Player” or “Observer” every 15 seconds.

2) Measurement

We put the NIRS sensors consisted of 16 Source-Detector pairs (16 channels) on the forehead and recorded brain activities of the each subject with NIRS system (Spectratech, Inc., Japan) simultaneously. We recorded electrocardiogram for heart rate (HR) and galvanic skin response (GSR) with Polymate II (Miyuki Giken, Japan) to evaluate their autonomic nerve function. After all tasks, they recall and reported their thinking or ideas by reviewing a video recorded their experiments.

Results

OxyHb which reflects brain activity did not show elevated activation when nothing came to the subject’s mind. Once the subject developed a strategy and got motivated, oxyHb showed a tendency to elevate activation in both player and observer period in all subjects. OxyHb was getting decreased when the subject solved the task or understood the strategy.

HR variation and GSR showed more changes in player period, compared to in observer period.

Discussion

Our NIRS results showed what’s happened in their neural behavior when the subjects were participating in a collaborate task. When the collaborate task worked for the subject, he or she was able to solve the task by thinking on his/her own even if the partner was taking the wrong way. This study may suggest the effectiveness of learning from the other and show the biological reaction caused by it.

Disclosures: **M. Yamazaki:** None. **N. Okamoto:** None. **Y. Kuroda:** None. **H. Eda:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

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Program #/Poster #: 091.14/JJJ13

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R01HD088417

Title: Rotation and Translation accuracy of VIVE trackers

Authors: **S. M. J. VAN DER VEEN**¹, **M. BORDELEAU**², **C. R. FRANCE**¹, **P. E. PIDCOE**³,
***J. S. THOMAS**¹

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Abstract: The golden standard for movement analysis is generally is 3D kinematics with optoelectric camera systems. The recent development of virtual reality (VR) with accompanying

motion tracking capabilities could reduce valuable time in participant setup and data processing. However, the accuracy of the VR systems must first be established. The aim of this study is to determine the accuracy of motion tracking with HTC VIVE trackers compared to data collected with Vicon Bonita cameras.

The 6-DOF information (i.e., translation and rotation about the X, Y, and Z axes) were collected simultaneously at 100 Hz using VIVE trackers and Vicon marker clusters mounted on a calibration rig using custom 3D printed parts. The calibration rig allowed for rotation about 2 axes (Y, Z) which correspond to flexion and axial rotation in our laboratory reference frame. We assessed 3 magnitudes of rotation about the Y axis (i.e., 15, 30, 60 °) combined with 3 rotations about the Z axis of 0, 15, and 45°. The RMS error between the two signals was determined and the difference between the VIVE and Vicon kinematic data relative to the calibration rig was calculated using custom MATLAB software.

When rotating around one axis (Y) the average differences between VIVE and Vicon were small with an average RMS of the angular data of 0.7° and 0.06mm of translation. However, with concomitant rotation of 15° and 45° around the Z axes, RMS of the angular data were 1.3° and 6.1° and translation of 0.9 mm and 0.7mm respectively. The difference between the expected angle and the measured angle was on average smaller around the Y axes in VIVE (1.3°) than Vicon (4.0°), but around the Z axes Vicon (1.1°) was more accurate than VIVE (-4.1°).

When rotation is constrained to a single axis, RMS error and differences in absolute angles between VIVE and Vicon are quite small. However, with concomitant rotation around the Z axis, the data from the VIVE system is more closely aligned with known changes in orientation from the calibration rig compared to the Vicon system. These findings indicate the VIVE system provides suitable accuracy for measuring human motion.

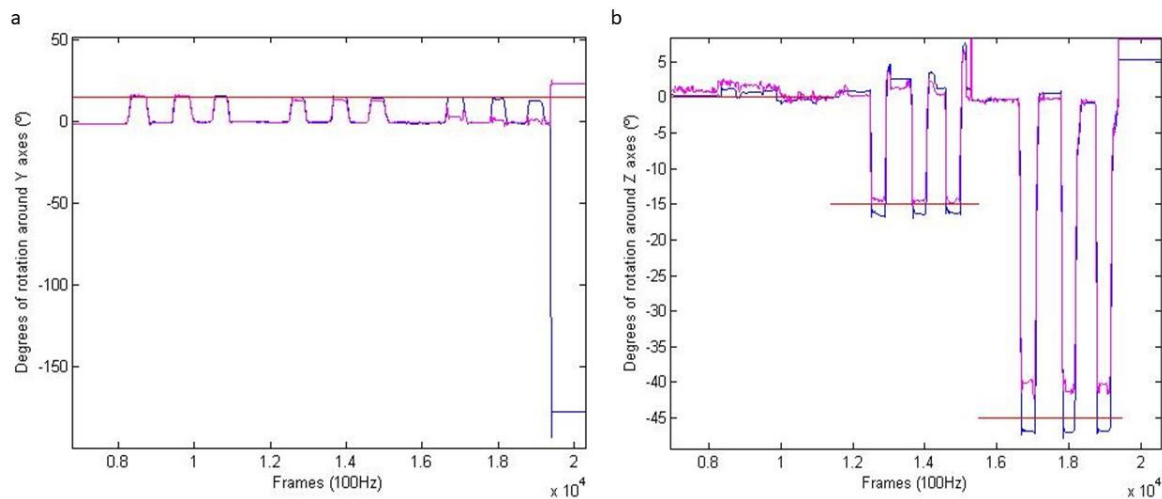


Figure 1. 15 degrees of rotation around the Y combined with 0, 15 and 45 degrees of rotation around the Z axes measured with Vicon (purple) and VIVE (blue). Figure a) represents the angles measured along the Y axes and b) represents angles measured around the Z axes.

Disclosures: S.M.J. van der Veen: None. **M. Bordeleau:** None. **C.R. France:** None. **P.E. Pidcoe:** None. **J.S. Thomas:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01 NS045193

NIH R01 MH115750

New Jersey Brain Injury Research Fellowship

NIH F31 NS089303

Nancy Lurie Marks Family Foundation

National Science Foundation Graduate Research Fellowship DGE-1148900

Title: Automated video-based clustering of mouse posture reveals individualized behavioral dynamics

Authors: ***L. WILLMORE**¹, M. KISLIN^{1,2}, J. VERPEUT^{1,2}, T. J. PISANO¹, B.-C. CHO¹, T. D. PEREIRA¹, D. E. ALDARONDO¹, S. RAVINDRANATH¹, M. MURTHY¹, J. SHAEVITZ^{3,4}, S. S.-H. WANG^{1,2}

¹Neurosci. Inst., ²Dept. of Mol. Biol., Princeton Univ., Princeton, NJ; ³Physics, Princeton Univ., Princeton, New Jersey, NJ; ⁴Lewis Sigler Inst. for Integrative Genomics, Princeton Univ., Princeton, NJ

Abstract: Improvements in behavioral monitoring and image processing have opened the way for systems neuroscientists to investigate animal behavior in natural environments. To build an unbiased lexicon of behavior states and their transition probabilities in mice, we designed an automated pose-tracking pipeline for clustering behaviors. This computational approach consists of five stages: (a) acquisition of high-resolution videos from freely-moving mice, (b) detection of body part positions using a convolutional neural network, (c) wavelet transform to capture behavioral dynamics on multiple time scales, (d) t-SNE embedding, and (e) watershed segmentation to form discrete clusters of stereotyped behaviors (adapted from Berman, Gordon J. et al. 2014, *J. R. Soc. Interface*). We found approximately 30 clusters representing distinct actions recognizable in two ways: (1) visual inspection of the video segments and (2) consistent enrichment of specific power bands in the wavelet spectra for specific body parts. These behaviors could be grouped into broader categories such as resting, grooming, walking, and running.

Comparing the pattern of cluster occupancy and transition statistics between individual mice revealed unique behavioral signatures indicative of an animal's temperament and inclination toward exploration. The behavioral signatures of individual mice also changed over the course of a 10-minute habituation period. We are now applying our method to investigate the effects of

chemogenetic inactivation of lateral posterior cerebellum (crus I), a region which projects to prefrontal and posterior parietal cortex and which is necessary for social preference, evidence accumulation, and novelty-seeking behavior. Unbiased classification methods allow for a detailed characterization of behavior in unrestrained mice and open the way for naturalistic investigation of neuropsychiatric disease and stress models.

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Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01 NS104899-01 BRAIN Initiative Award (M.M. and J.S.)

HHMI Faculty Scholar Award (M.M.)

National Science Foundation Graduate Research Fellowship DGE-1148900

Title: Fast estimation of animal pose using deep neural networks

Authors: ***T. D. PEREIRA**¹, D. E. ALDARONDO¹, J. SHAEVITZ^{2,3,1}, M. MURTHY^{1,4}

¹Neurosci., ²Physics, ³Lewis Sigler Inst. for Integrative Genomics, ⁴Biol., Princeton Univ., Princeton, NJ

Abstract: Connecting neural activity with behavior requires methods to parse what an animal does into its constituent components (the movements of its body parts), which can then be connected with the electrical activity that generates each action. Recent developments in the unsupervised clustering of postural dynamics made significant inroads into defining the set of behaviors performed by an animal. A major drawback to these techniques to date has been their reliance on PCA to reduce the dimensionality of an image time series such that information about which parts of the body are used in each behavior is lost. To address this issue, we turned to deep learning-based methods for pose estimation. We automatically predict the positions of animal body parts via iterative training of a deep convolutional neural network with as little as 10 frames of labeled data for initial prediction and training. Our framework consists of a graphical interface for interactive labeling of ground truth body-part positions as well as software for efficient training of a convolutional neural network on a workstation with a modern GPU (<1 hour) and fast prediction on new data (up to 185 frames per second). We validate the results of our method using a previously published dataset of high quality videos of freely behaving adult fruit flies (*Drosophila melanogaster*), and recapitulate a number of reported findings on insect

gait dynamics. We show its applicability as a front end to an unsupervised behavioral classification algorithm and demonstrate how it can be used to describe stereotyped behaviors in terms of the dynamics of individual body parts. Finally, we apply the method to more challenging imaging situations (a large dataset of pairs of flies imaged on backgrounds of mesh and microphones) and use it to quantify the pose dynamics of male and female flies during acoustic communication behaviors that occur as part of the courtship ritual.

Disclosures: T.D. Pereira: None. D.E. Aldarondo: None. J. Shaevitz: None. M. Murthy: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.17/JJJ16

Topic: I.06. Computation, Modeling, and Simulation

Title: Rehabilitation stick can show the movement character and the outcome of trials

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Abstract: Introduction

For rehabilitation research, the effective tools were required. We have developed a new rehabilitation tool.

When an angle between a coordinate of the body and a coordinate of operation was shifted, subjects need to correct an angle to achieve cursor movement task. Our hypothesis is that an angler distribution of the achievement time and its change denote the movement characteristic and an outcome of the trials.

Method

We prepared an arm rehabilitation tool (R-stick). The stick, attached to the circular stand, made it possible to incline in all the directions with ball joint technology. The inclination of the stick was detected and we could move the cursor presenting on the PC screen. The R-Stick coordinate angle was set up by changing the direction of the stand. When the angle was 0 degrees, the coordinate of the body and the coordinate of operation were the same.

The subject sat on a chair, and was required to move the cursor from the center to the upward of the screen. At the first trial the angle was set to 0 degrees, and it was repeated five times. After the first trial the angle was changed to the different angle (45, 90, 135, 180, 225, 270, 315, 360 degrees) random. We measured the duration time in each angle trial.

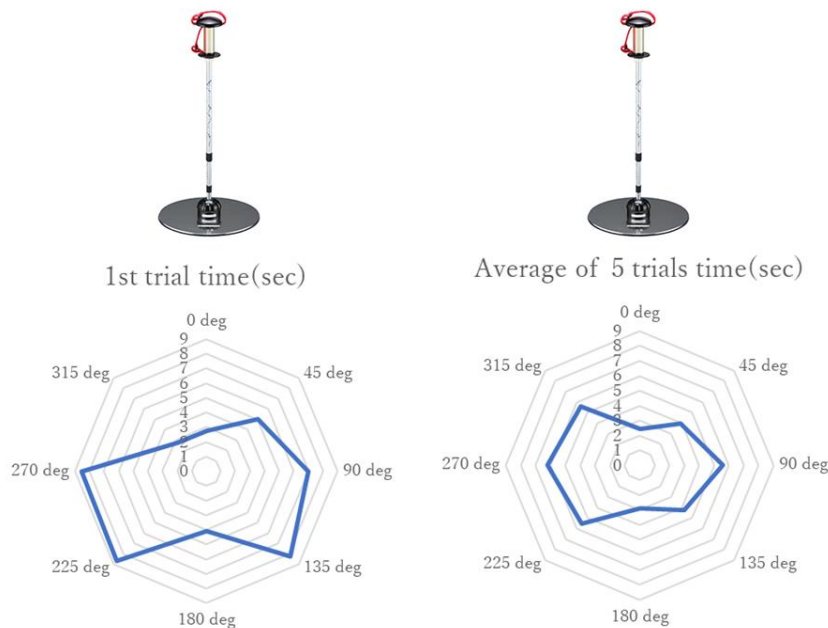
Results

Trial times were displayed by the radar chart. This radar chart shows the time of cursor

movement from the center to the upward, and the angles to be corrected to move cursor upward. The radar chart of the mean of five trials with different view angle varied from that of the first trial.

Discussion

The radar chart showed the individual movement character. When the trial was repeated, radar charts differed, which showed that the character was changed. Visualizing the characteristics of the patient's movement and arranging their rehabilitation by optimized individual performance will make the outcome effective.



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Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.18/JJJ17

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH/NIGMS U54GM104942

Title: Realistic biomechanical lower-limb model implemented for human-in-the-loop applications

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Abstract: Individuals with locomotor deficits frequently suffer a decrease in quality of life when the neural or musculoskeletal systems are damaged, often promoting comorbidities like obesity and depression. Novel biomechanical tools (e.g. OpenSim) allow the holistic examination of motor control mechanisms using musculoskeletal models. However, model complexity is negatively correlated with the validity of simulated limb dynamics, which is crucial for human-in-the-loop myoelectric prostheses. Furthermore, additional validation is required for both the function and structure captured in the model. Our goal in this study was to develop a robust lower-limb model for real-time control applications by employing empirical data and multidimensional generalizations of muscle structure. We combined two previous models available from the OpenSim community (Hamner et al., 2010; Rajagopal et al., 2016) to represent 14 degrees of freedom (DOF) for the lower-limbs. The combined model had large discrepancies in muscle parameters compared to published measurements composed from over 20 studies. These discrepancies were resolved by iteratively adjusting the muscle paths of the 43 musculotendon actuators spanning the hip, knee, ankle and toe joints for each leg until the simulated profiles matched experimental data at least with R^2 above 0.49. Moreover, the simulated profiles were converted into polynomial approximations representing muscle lengths and moment arms as functions of joint angles to optimize execution speed with low fitting error (less than 1% error). We used these approximations for an automated search within the large multidimensional domain (9 points per muscle spanning on average 3 DOFs is over 29,286 points) to identify errors in unobserved relationships between muscle parameters and limb postures, e.g. change in moment arm sign. Once these identified errors were corrected using the iterative procedure above, the relative scaling of maximum force muscle parameters for Hill-type muscle models were validated against maximum voluntary contraction measurements. Next, the musculoskeletal model's control capability was tested using MATLAB and MuJoCo simulation environments. During testing, our optimized model successfully transformed surface electromyography activity into movement with accurate forward dynamics in real-time (less than 2 ms loop time), demonstrating that this implementation can resolve dynamic lower-limb nonlinearities and support biomimetic prostheses. Thus, we hope this study can improve current myoelectric prosthetic control and rehabilitation.

Disclosures: T. Moon: None. M.T. Boots: None. A. Sobinov: None. S. Yakovenko: None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.19/JJJ18

Topic: I.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI Grant Numbers JP17H02642, JP16K04286

Title: The long term exposure to learning activity with strong sense of weak point affects the autonomic nerve activity. - Pilot study to elucidate the actual situation of dyslexia student at university -

Authors: *A. KAWASAKI¹, T. TAKAHASHI⁴, Y. MATSUZAKI², H. TAKEUCHI³, M. NAKAGAWA⁵

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Abstract: Introduction

According to the investigation for child, the prevalence of dyslexia in the Japanese speaker is about 6 to 7 %. However, the actual situation of dyslexia in the higher education has not been clarified. The students who were confirmed with localized learning disorder are only 0.005 % (Japan Student Service Organization, 2018). It is assumed that there is difference about the symptom of dyslexia between childhood and in youth. Current study investigated the influence of reading disability to independence nerve activity as one of the actual situation elucidation of dyslexia at the universities. We inspected the hypothesis “sense of weak point by the accumulation of the failure experience of the childhood has more significant influence on autonomic nerve, especially on parasympathetic nerve degree than performance”.

Methods

The subjects are 31 university students(age 21.51±1.18). We adopted the reading and writing support needs scale as a measure of subjects’ consciousness about weak point of their reading. This scale was 4-point scale (applicable 4~ inapplicable1) and consisted of 29 items. And we used non-language naming task from reading and writing fluency task (Takahashi, 2018) to estimate subjects’ actual reading difficulty. To measure a change of independence nerve activity during reading aloud, we adopted the pulse(TAS9view:YKC.Ink). We measured HR, LH/HF and pNN50(%) to assume the average volatility before problem enforcement and under problem enforcement as index.

Results

The nonword reading aloud time required was 37.16±6.79 (M±1SD). There existed 3 subjects who showed delays more than +2SD average (maximum 79 seconds). The score of reading and writing support needs scale was 57.45±11.34 (M±1SD). The mean of LH/HF during a reading task was 2.43~3.70. All of them were over 1. In pNN50(%), 11 students showed an upward trend at the time of problem enforcement in comparison with a resting period. On the contrary, 20 students showed a downswing. As a result of Clause 2 logistic-regression analysis, with assuming the amount of change of pNN50(%) at the time of reading aloud a dependent variable, weak point awareness score and reading score an independent variable, reading score ($\beta=1.02$, $p<.10$), weak point awareness was significant($\beta=1.48$, $p<.05$).

Consideration

We showed that in university student, consciousness about own weak point of reading problem

gives bigger influence to independence nerve activity than actual performance. This result matches the recent study (Grassman et al., 2016), which has suggested the interposition of the uneasy tendency in the relation with problem accomplishment and the automatic nerve activity.

Disclosures: **A. Kawasaki:** None. **T. Takahashi:** None. **Y. Matsuzaki:** None. **H. Takeuchi:** None. **M. Nakagawa:** None.

Poster

091. Data Analysis and Statistics: Human Data: Vision, Audition, Movement, and Posture

Location: SDCC Halls B-H

Time: Saturday, November 3, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 091.20/JJJ19

Topic: I.06. Computation, Modeling, and Simulation

Title: The difference of the involvement in visual attention lead to different results in the performance of the eye movement function

Authors: ***T. KAWADA**¹, **A. KAWASAKI**¹, **T. TAKAHASHI**²
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Abstract: INTRODUCTION

Developmental Eye Movement Test(DEM) is one of the most common neuropsychological test for eye movement function(Garzia RP et al, 1990). Its application range has been expanded not only to ocular motility disorder but also to developmental disorders such as dyslexia(Okumura et al, 2017). Eye movement function is closely related to visual working memory and visual attention (bottom-up process and top-down process). Because the results differ depending on the type of stimulus and the presentation method, careful interpretation is required.

DEM is highly related to visual attention tasks, especially top-down process tasks(Kawada et al, 2018). In this time we newly developed a new task focusing on eye movement function based on bottom-up process attention. Top-down process attention is involved in the bilateral dorsolateral prefrontal cortex, bottom-up process attention further involves the right ventrolateral prefrontal cortex. In this study, we discuss the relationship between visual attention and eye movement function from the relation between measurement result of f-NIRS undergoing both tasks and reading task(silent reading and reading aloud).

METHOD

We adopted DEM and Follow a Index with Eye Movement (FIEM) as eye movement function evaluation. FIEM is a task to align the line of sight with the index appearing randomly on the monitor for 60 seconds. And the number of matches, the total eye movement distance, and its efficiency were used as index.

We used Tobii eye tracker 4c manufactured by Tobii for measurement of eye movement. The reading task used the reading task created by Takahashi (2018).

Evaluation of eye movement function and activation of bilateral prefrontal cortex during reading

aloud were measured by NIRS (astem, Hb 131 S). The target is 21 adults (21 to 27). Eye disorders and SLD persons are not included.

RESULT

DEM correlated silent reading (.297) and FIEM correlated reading aloud (.581) and DEM and FIEM were uncorrelated (-.027). In FIEM, the correlation between the number of matches and the total eye movement distance was -.250, confirming the validity as eye movement test. There was no difference in the relative activation of bilateral prefrontal cortex between FIEM and DEM.

DISCUSSION

It was suggested that there is a difference in the involvement of visual attention in the difference between DEM and FIEM than the relation between visual attention and eye movement function. Detailed analysis will be continued so that further verification by NIRS will be possible in the future.

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