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Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH support to J.R.S. and Y.R.P.
NIH/NEI 5T32EY007143-20 to R.E.J.
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R01EY027713 to A.L.K.
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Title: Fezf1 determines the fate of ON versus OFF starburst amacrine cells

Authors: *R. E. J. JAMES-ESPOSITO[1], Y.-R. PENG[2], W. YAN[2], J. N. KAY[4], J. R. SANES[3], A. L. KOLODKIN[1];
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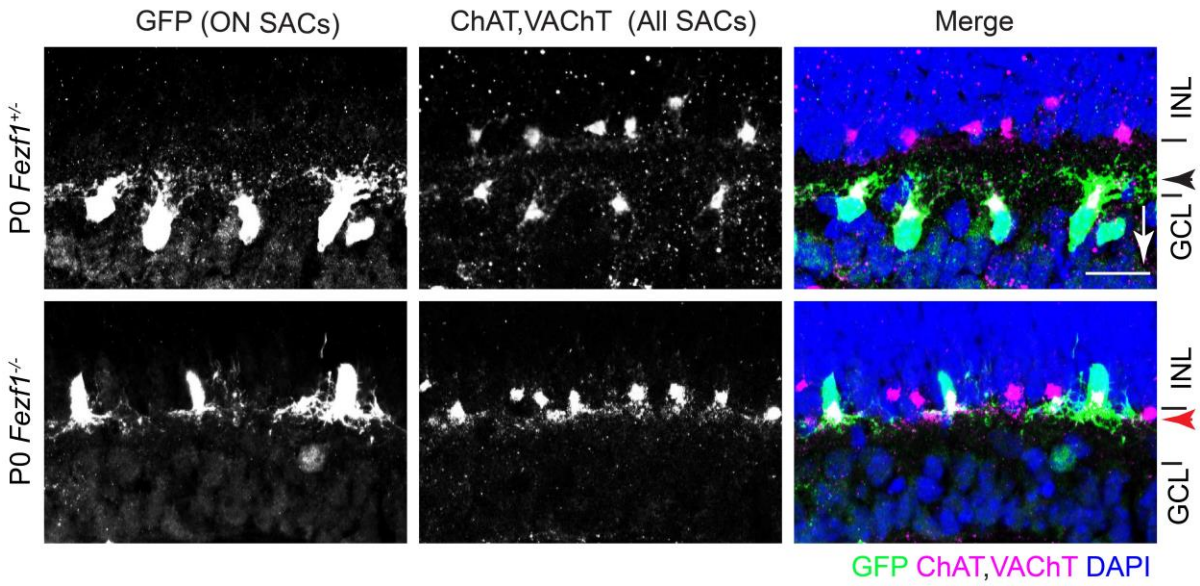
Abstract: Among the numerous neuronal types in the central nervous system are pairs of types that are extremely similar, but differ in some key feature. In the vertebrate retina, dendrites of these so-called paramorphic pairs stratify at different levels within the inner plexiform layer (IPL), and therefore have different synaptic partners. How do these types become distinct? Here, we address this issue with respect to starburst amacrine cells (SACs). SACs are crucial for computing the direction of moving objects and for generating the optokinetic response. They come in ON (responsive to light onset) and OFF (light offset) subtypes, with dendrites in the ON and OFF sublaminae of the IPL and somata in the ganglion cell layer (GCL) and inner nuclear layer (INL), respectively. Using single-cell mRNA sequencing, we discovered that ON and OFF SACs are transcriptionally distinct subtypes by embryonic day 16 (E16), before their somata have segregated or their dendritic arbors have formed. We show that the transcriptional repressor FEZ Family Zinc Finger 1 (*Fezf1*) is selectively expressed by postmitotic ON SACs at the boundary between the outer neuroblastic and inner neuroblastic layers (ONBL and INBL) at E14.5. In *Fezf1* mutants, ON SACs fail to migrate into the INBL (the developing GCL), and their polarity is flipped such that they arborize their dendrites in the apical layers of the nascent IPL, similar to OFF SACs. We find that *Fezf1* is required for repression of atypical Rho GTPase 3 (*Rnd3*) in ON SACs, which promotes SAC migration into the INBL. Moreover, we find that in the absence of *Fezf1*, ‘ON’ SACs express OFF genes and lose the expression of ON genes, thus adopting an ‘OFF’ phenotype. These results show that ON and OFF SACs become distinct at an early stage in retinal development via the selective expression of *Fezf1*, which in turn directs a

transcriptional program that determines the distinct somatic and dendritic positions of these closely related amacrine cells.



Disclosures: **R.E.J. James-Esposito:** None. **Y. Peng:** None. **W. Yan:** None. **J.N. Kay:** None. **J.R. Sanes:** None. **A.L. Kolodkin:** None.

Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01 DC015903

Title: Trans-differentiation of cochlear outer hair cells into inner hair cells in the absence of INSM1

Authors: *J. GARCIA-ANOVEROS[1], T. WIWATPANIT[2], S. M. LORENZEN[2], J. A. CANTU[2], C. Z. FOO[2], J. C. CLANCY[2], M. CHEATHAM[3], A. DUGGAN[4];
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Abstract: The mammalian cochlea contains two types of mechanosensory hair cells that play different and critical roles in hearing. Inner hair cells (IHCs), with an elaborate presynaptic apparatus, signal to cochlear neurons and communicate sound information to the brain. Outer

hair cells (OHCs), equipped for electromotility, mechanically amplify sound-induced vibrations, enabling enhanced sensitivity to sound and sharp tuning. Cochlear hair cells are solely generated during development and their death, most often of OHCs, is the main cause of deafness. Hence, attempts to revert many cases of hearing loss should aim at generating OHCs. OHCs and IHCs, together with supporting cells, originate embryonically from the prosensory region of the otocyst, but how hair cells differentiate into two different types is unknown. Here we show that *Insm1*, which encodes a zinc finger protein transiently expressed in nascent OHCs, consolidates their fate by preventing trans-differentiation into IHCs (1). In the absence of INSM1 many hair cells born embryonically as OHCs switch fates towards late embryogenesis (~E17) and proceed to differentiate into mature IHCs. The OHC to IHC conversion was more frequent in the neural (medial, closer to the IHC row) than abneural (lateral, further from the IHCs) rows, suggesting an IHC-inducing gradient in cochlear development to which OHCs are normally unresponsive, but become responsive in the absence of INSM1. In order to identify the genetic mechanisms by which *Insm1* operates, we compared transcriptomes of immature IHCs vs OHCs, as well as OHCs with and without INSM1. We find that OHCs lacking INSM1 upregulate a set of genes, most of which are normally preferentially expressed by IHCs. The homeotic cell transformation of OHCs without INSM1 into IHCs reveals for the first time a mechanism by which these neighboring mechanosensory cells begin to differ: INSM1 represses a core set of early IHC-enriched genes in embryonic OHCs, so that they proceed to mature as OHCs. INSM1 thus consolidates the fate of OHCs during a critical period of their early development. Without INSM1, many of the OHCs upregulating these few IHC-enriched transcripts trans-differentiate into IHCs. Because the misexpression of these IHC-enriched genes in early OHCs underlies their trans-differentiation into IHCs, these genes likely include the regulators driving IHC-specific differentiation. (1) Wiwatpanit, T., Lorenzen, S. M, Cantú, J. A., Foo, C. Z., Hogan, A. K., Márquez, F., Clancy, J. C., Schipma, M. J., Cheatham, M., Duggan, A., and García-Añoveros, J. (2018) Trans-Differentiation of Outer Hair Cells into Inner Hair Cells in the Absence of INSM1. *Nature* 563, 691-695.

Disclosures: **J. Garcia-Anoveros:** None. **T. Wiwatpanit:** None. **S.M. Lorenzen:** None. **J.A. Cantu:** None. **C.Z. Foo:** None. **J.C. Clancy:** None. **M. Cheatham:** None. **A. Duggan:** None.

Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.03

Topic: A.01. Neurogenesis and Gliogenesis

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VA grant 5I01 BX000252
Shurl and Kay Curci Foundation

LoGlio Foundation
Hana Jabsheh Initiative to (D.A.L.)

Title: Maintenance of neural stem cell positional identity by mixed-lineage leukemia 1

Authors: *R. N. DELGADO[1], B. MANKSY[1], C. LU[1], R. ANDERSEN[1], S. HAMID[2], Y. DOU[4], A. ALVAREZ-BUYLLA[3], D. LIM[5];
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Abstract: In both the embryonic and postnatal brain, neural stem cells (NSCs) have distinct positional identities that determine the subtypes of neurons they can generate. Early in development, morphogens provide positional information to NSCs in the neural tube, inducing the expression of region-specific transcription factors. Despite vast increases in size and morphological complexity of the developing brain, the positional identity of NSCs—which is critical for generating the proper diversity of neurons in the mature brain—is maintained. However, the mechanisms by which differences in NSC positional identity are maintained throughout embryonic and postnatal development are poorly understood. Here we demonstrate that the positional identity of ventral mouse NSCs is dependent on an epigenetic memory system that includes *Mixed-lineage leukemia 1 (Mll1)*. While we found that Shh-signaling is not required to maintain *Nkx2-1* expression in ventral NSCs, conditional deletion of *Mll1* results in the progressive loss of NSC ventral identity both *in vivo* and *in vitro*. Thus, following its initial induction, ventral NSC positional identity is maintained by MLL1 independent of Shh-signaling. More generally, our results support a model in which key aspects of dorsal-ventral positional identity imposed early in embryogenesis are epigenetically maintained in NSCs over the course of development, thereby preserving NSC diversity necessary to make the full repertoire of neurons and glia from embryonic to postnatal life.

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Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1U01MH114825-01

Title: Single-cell transcriptomic analysis of human cortical development throughout the prenatal and postnatal life

Authors: *D. VELMESHEV[1], D. JUNG[1], A. BHADURI[1], M. HAEUSSLER[2], L. SCHIRMER[3], S. WANG[1], Y. PEREZ[1], N. GOYAL[4], M. PAREDES[1], E. HUANG[1], A. KRIEGSTEIN[1];
[1]Neurol., UCSF, San Fancisco, CA; [2]Univ. of California, Santa Cruz, Santa Cruz, CA; [3]Univ. Med. Ctr. Mannheim, Mannheim, Germany; [4]Univ. of California, Berkeley, Berkeley, CA

Abstract: Human cortical development spans years of prenatal and postnatal development. This incredibly complex process involves multiple interacting cell lineages and dynamic processes, such as neurogenesis and gliogenesis, neuronal migration, cell differentiation, areal specification, axon outgrowth and synapse formation and maturation. Human cortical development proceeds through a number of critical stages that are believed to be affected in neurodevelopmental and psychiatric diseases, such as autism spectrum disorder and schizophrenia. In order to investigate the dynamic landscape of human cortical development at the single-cell resolution, we utilized single-nucleus RNA sequencing (snRNA-seq) to profile more than 100 post-mortem human cortical tissue samples from over 50 individuals and three cortical areas. We included samples ranging from second and third trimesters of prenatal development though neonatal and early postnatal stages to teenage and early adult years. By using unbiased nuclei isolation coupled with droplet-based single-cell profiling (10x Genomics), we generated over 300,000 single-nucleus transcriptomics profiles. We performed unbiased clustering, marker discovery and trajectory analysis, and were able to discover gene expression programs that underlie generation of subtypes of cortical projection neurons, interneurons and glial cell types, as well as critical process of development, such as generation of astrocytes, axon outgrowth, synapse formation and formation of mature cortical neuronal circuits. By intersecting cell type-specific developmental gene expression profiles with known genetic risk factors of neurodevelopmental disorders, we were able to identify cell types and developmental stages that can be especially affected in autism spectrum disorder and schizophrenia, leading to improper formation and function of specific cortical circuits. Our study sheds light on cell type-specific mechanisms of normal cortical development and cell types and processes affected in common neurodevelopmental disease. In addition, our rich single-nucleus transcriptomic atlas will be of great value to a wide range of neuroscientists.

Disclosures: **D. Velmeshev:** None. **D. Jung:** None. **A. Bhaduri:** None. **M. Haeussler:** None. **L. Schirmer:** None. **S. Wang:** None. **Y. Perez:** None. **N. Goyal:** None. **M. Paredes:** None. **E. Huang:** None. **A. Kriegstein:** None.

Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant U01 MH105989
NIH Grant R35 NS097305

Title: Human embryonic OPCs and white matter expansion

Authors: *W. HUANG[1], A. BHADURI[1], D. VELMESHEV[3], A. R. KRIEGSTEIN[2];
[2]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., [1]Univ. of California San Francisco, San Francisco, CA; [3]Neurology/Regeneration Med., UCSF, San Francisco, CA

Abstract: During evolution, both the white matter and grey matter of the human cerebral cortex enlarge greatly. Previous studies showed that both oRGs and IPCs play important roles in the human neurogenesis and grey matter expansion. But the mechanisms of the human oligodendrogenesis and white matter expansion remain largely unknown. Here by single-cell RNA-seq of live human cortical cells and IHC on fixed human brain slices in the late 2nd trimester, we find evidences for local generation of OPCs in the developing cortex. Moreover, we find lineage-committed IPCs (O-IPCs) that produce OPCs in the human cortex. We also reconstruct the developmental trajectory of oligodendrogenesis and interpret the lineage relationship between neurogenesis and gliogenesis. Further studies on cultured brain slices indicate that OPC marker PCDH15 is required for the daughter cell separation after OPC division, while both O-IPCs and OPCs in the embryonic human brain undergo multiple rounds of division and act as transit amplifier to increase the progenitor cell pool, which might contribute to the white matter expansion.

Disclosures: W. Huang: None. **A. Bhaduri:** None. **D. Velmeshev:** None. **A.R. Kriegstein:** None.

Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.06

Topic: A.03. Stem Cells and Reprogramming

Support: NIH grant AG045656
Charles H. “Skip” Smith Endowment Fund at Pennsylvania State University to G.C.

Title: A gene therapy approach to directly convert striatal astrocytes into GABAergic neurons in a mouse model of Huntington’s disease

Authors: *Z. WU, M. PARRY, X. HOU, H. WANG, R. CAIN, Z. PEI, Z. GUO, G. CHEN;
Biol., Penn State Univ., University Park, PA

Abstract: Huntington's disease (HD) is an autosomal degenerative disease typically caused by Huntingtin (Htt) gene mutation resulting in extra CAG repeats and Htt protein aggregates. The GABAergic neurons in the striatum are particularly vulnerable to the mutant Htt (mHtt) toxicity and often degenerate early causing motor and cognitive functional deficits. Previous studies have achieved partial success in reducing mHtt level through antisense oligonucleotides or gene editing methods, or in regenerating striatal neurons through cell transplantation technology. However, so far there is still no disease-modifying therapy available to treat HD patients. In this study, we report an *in vivo* cell conversion technology to regenerate striatal GABAergic neurons in the R6/2 mouse model for HD. This gene therapy approach is achieved through AAV2/5 mediated ectopic expression of two transcription factors, NeuroD1 and Dlx2, in the striatal astrocytes to directly convert them into DARPP32$^+$ GABAergic neurons. We found that the astrocyte-to-neuron conversion rate in the striatum reached 80% and over 50% of the converted neurons were DARPP32$^+$. Electrophysiological studies revealed similar functional properties between the astrocyte-converted neurons and their neighboring preexisting neurons, including a similar action potential firing pattern and robust synaptic events. Moreover, the striatal astrocyte-converted neurons projected to target areas including the globus pallidus and the substantia nigra in a time-dependent manner. Behavioral analyses found that compared to the control group, the NeuroD1 and Dlx2-treated R6/2 mice showed a significant extension of life span and improvement of motor functions. Together, this study demonstrates that *in vivo* direct conversion of striatal astrocytes into DARPP32$^+$ GABAergic neurons may be a potential disease-modifying therapy to treat HD and other neurodegenerative disorders.

Disclosures: Z. Wu: None. **M. Parry:** None. **X. Hou:** None. **H. Wang:** None. **R. Cain:** None. **Z. Pei:** None. **Z. Guo:** None. **G. Chen:** None.

Nanosymposium

010. In Vivo Studies of Stem Cell Fate

Location: Room S404

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 010.07

Topic: A.03. Stem Cells and Reprogramming

Support: NIH NS100514

Title: Assessing *in vivo* neuronal reprogramming by automated, resonance-scanned confocal virtual tissue image acquisition and artificial intelligence-assisted stereology

Authors: *D. A. PETERSON[1,2], R. A. MARR[3], M. THAQI[1];
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IL; [2]NeuroRenew, Inc., Chicago, IL; [3]Neurosci., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Direct *in vivo* reprogramming of non-neuronal cells in the mature CNS into phenotypically correct neurons can be achieved through forced expression of pioneering transcription factors, such as Ngn2, NeuroD1, and Ascl1, that normally act to direct neuronal fate specification during development. This process produces a variable population of induced neurons that can be identified through their expression of reporter genes tied to the induction process and expression of various neuronal phenotypic markers, requiring detection of multiple fluorescence labels with resolution by confocal microscopy. Following *in vivo* gene delivery of lineage instruction factors, the number of infected cells and their distribution present some challenges for accurate quantitation by design-based stereological sampling. Generally, too many cells are infected to completely count with accuracy across histological sections arguing for subsampling of the population by stereological principles. In addition, cell density varies widely from the site of injection to the most distant infected cells. This means that sampling frequency density must be high to reduce estimator variance to an acceptable level. Furthermore, traditional acquisition of confocal stacks is time consuming and inefficient. The recent availability of resonance scanning confocal microscopes permits the rapid generation of virtual section data sets. Efficient sampling design can now follow complete image acquisition of the histological material. The application of artificial intelligence to detecting cells with different label combinations within the virtual section data set makes it possible to automate cell counting if detection criteria can be achieved. However, cell detection must be combined with stereological sampling principles to account for sectioning and other artifacts and to accommodate fractionated sampling. These approaches are appropriate for other “rare” cell populations, such as grafted cells, and could be extended to dense cell populations if shown to be efficient.

Disclosures: D.A. Peterson: None. **R.A. Marr:** None. **M. Thaqi:** None.

Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.01

Topic: A.10. Development and Evolution

Support: NIH Grant P51-OD011132
Center for Childhood Infections and Vaccines of Emory University and Children's Healthcare of Atlanta

Title: Postnatal zika virus infection causes long-term neurodevelopmental consequences in infant rhesus macaques

Authors: *J. RAPER[1,2], Z. KOVACS-BALINT[1], M. MAVIGNER[2], S. GUMBER[1], M. SANCHEZ[1,3], M. ALVARADO[1], A. CHAHROUDI[2,4];
[1]Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [2]Pediatrics, [3]Psychiatry and Behavioral Sci., Emory Univ. Sch. of Med., Atlanta, GA; [4]Childrens Healthcare of Atlanta, Atlanta, GA

Abstract: To date, most studies have focused on the impact of zika virus (ZIKV) infection in utero, documenting its association with microcephaly, fetal brain lesions, and other serious birth defects. Considering the impact that ZIKV infection can have on the developing nervous system and given that the postnatal period is also a time of rapid brain growth, it is important to understand the potential neurodevelopmental consequences of ZIKV infection during infancy. To address this question, we used a highly clinically relevant rhesus macaque (RM) model. We longitudinally monitored four infant RM through 12 months of age with neuroimaging, behavioral and neurohistopathology assessments. Two RMs were infected with ZIKV at 5 weeks of age and two were age-, sex-, and rearing-matched uninfected controls. Postnatal ZIKV infection resulted in long-term behavioral changes, including increased emotional reactivity, decreased social contact, increased slips and falls, as well as visual recognition memory deficits at one year of age. Structural and functional magnetic resonance imaging (MRI) demonstrated that ZIKV-infected infant RMs had persistent enlargement of lateral ventricles, smaller amygdalae, hippocampi, and putamen, as well as altered functional connectivity between brain areas important for socioemotional behavior and cognitive function. These structural and functional brain changes may explain the observed alterations in socioemotional behavior and learning and memory function. Although ZIKV was quickly cleared from plasma within 7 days post-infection, at 12 months of age neurohistopathology showed signs of brain lesions. One ZIKV infected RM showed persistent mild neuronal and perivascular calcification in the putamen and the other presented enlarged lateral ventricle of the occipital lobe. These neurohistopathology findings confirm and validate the alterations in structural and functional neuroimaging, including weak functional connectivity between the putamen and inferior temporal cortex. Overall, this study demonstrated that postnatal ZIKV infection of infants in this model has long lasting neurodevelopmental consequences, which suggest that long-term clinical monitoring of pediatric cases is warranted.

Disclosures: J. Raper: None. **Z. Kovacs-Balint:** None. **M. Mavigner:** None. **S. Gumber:** None. **M. Sanchez:** None. **M. Alvarado:** None. **A. Chahroudi:** None.

Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.02

Topic: A.10. Development and Evolution

Support: 5P50MH106438

Title: Social and cognitive development in a nonhuman primate model of maternal immune activation

Authors: A. M. RYAN[1], A.-M. IOSIF[3], T. MURAI[6], C. E. HOGREFE[4], J. VAN DE WATER[4], A. K. MCALLISTER[5], C. S. CARTER[2], *M. D. BAUMAN[7];
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Abstract: Children born to women who experience infection during pregnancy have an increased risk of brain disorders with neurodevelopmental origins, including both schizophrenia (SZ) and autism spectrum disorder (ASD). Rodent models of maternal immune activation (MIA) have identified the maternal immune response as the critical link between maternal infection and aberrant brain and behavior development in offspring. The nonhuman primate MIA model provides an opportunity to maximize the translational utility of this model in a species more closely related to humans. Our previous pilot studies revealed alterations in brain and behavioral development in rhesus monkeys (*Macaca mulatta*) born to MIA-treated dams. Here we present emerging behavioral outcomes from a larger cohort of MIA-treated nonhuman primates. A modified form of the viral mimic, Polyinosinic-polycytidylic acid (PolyIC), was delivered to a new cohort of pregnant rhesus monkeys (N=14) in the late first trimester (gestational days 43, 44, 46) to stimulate a maternal immune response. Control dams received saline injections at the same gestational time points (N=10) or were untreated (N=4). MIA-treated dams exhibited a strong immune response as indexed by transient increases in sickness behavior, temperature and inflammatory cytokines. The offspring are undergoing ongoing comprehensive behavioral evaluations paired with longitudinal neuroimaging to quantify the emergence of brain and behavior pathology associated with prenatal maternal immune challenge. Although MIA-treated monkeys developed species-typical milestones and showed no overt signs of atypical interactions with mothers or peers, the MIA-treated animals demonstrated abnormal brain growth trajectories as early as six months of age. At two years of age, the animals were tested in a reversal learning paradigm that requires a subject to flexibly adjust its behavior when the reward-related contingencies that it has previously learned are reversed. All animals advanced and performed similarly on the training and initial discrimination phases of the test. However, on the first day of the initial reward reversal, the MIA-treated animals more frequently “balked” or failed to make a choice as compared to controls (Wilcoxon two-sample test p-value = .005). These emerging data suggest that MIA-treated animals exhibit subtle impairments in cognitive processing. Fine-grained analysis of social development, including non-invasive eye tracking data, will be presented to also explore the impact of MIA on social development.

Disclosures: M.D. Bauman: None. **A.M. Ryan:** None. **A. Iosif:** None. **T. Murai:** None. **C.E. Hogrefe:** None. **J. Van de Water:** None. **A.K. McAllister:** None. **C.S. Carter:** None.

Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.03

Topic: A.10. Development and Evolution

Support: IARS Grant

Title: Social behaviors and cognitive function in non-human primates 2 years after infant isoflurane exposure

Authors: *V. NEUDECKER[1], J. F. PEREZ-ZOGHBI[1], K. COLEMAN[2], M. NEURINGER[2], N. ROBERTSON[2], A. BEMIS[2], B. GLICKMAN[2], L. MARTIN[2], G. A. DISSEN[2], A. BRAMBRINK[1];
[1]Dept. of Anesthesiol., Columbia Univ. Med. Ctr., New York, NY; [2]Div. of Neurosci., ONPRC, Oregon Hlth. & Sci. Univ., Beaverton, OR

Abstract: Introduction: There is controversy whether exposure of young children to general anesthetics affects their neurobehavioral development. New clinical studies show that anesthesia exposure is not associated with lower intelligence quotient but may alter behaviors. In non-human primates (NHPs) infant anesthesia exposure causes acute widespread apoptosis of neurons and glial cells and later in life affects neurobehavioral development. We previously showed that 1-year-old NHPs who received general anesthesia as infants showed increased frequency of anxiety behaviors when freely moving in their home environment. Here we report the neurocognitive and behavioral assessments of the same cohort during the second year of life. Our hypothesis was that multiple, but not single exposure to isoflurane (ISO) during infancy impairs cognitive development and social behaviors later in life. **Methods.** 7-8 NHPs per group were exposed for 5 hours to ISO (1.8%, Vol%) either one time (1X) or three times (3X) at days 6, 9 and 12. Control animals were exposed to 30% oxygen. The one-year-old NHPs were weaned and housed in groups of 5-6 animals. Cognitive development was assessed during the second year of life using the delayed response test of spatial working memory and tests assessing cognitive flexibility. At two years of age, we assessed their response to everyday, naturalistic events in their home environment and inhibition and anxiety behaviors using the Novel Object Test (NOT) and the Human Intruder Test (HIT). Training, assessments and analyses were conducted blinded regarding treatments. Data are presented as means ± SD. ANOVA and Kruskal-Wallis tests were used. Preliminary observations from these assessments were reported earlier (Brambrink *et al.*, ASA 2016). **Results**. The cognitive testing did not reveal significant differences between groups. Home-cage testing revealed that NHPs in the 3X group spent significantly less time in close social contact than controls. NHPs in the 1X group were significantly more inhibited in their reaction towards novel objects, but not those in the 3X group. NHPs in the 1X group showed a trend towards more anxiety behavior in the HIT.

Conclusions: Single or multiple exposures to ISO do not cause impairments in working memory or cognitive flexibility tests during the second year of life. In contrast, multiple ISO exposures decreased affiliative social behavior in the home environment, while single exposure was associated with an increased behavioral inhibition in response to novel objects. Our findings agree with newest clinical studies reporting behavioral alterations in social settings and may guide design for future studies in the field.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.04

Topic: A.10. Development and Evolution

Support: NIH 2R01MH061285-16
NIMH T32MH018931-29

Title: Psychophysiological encoding of value signals in children exposed to abuse

Authors: *K. E. SMITH[1], S. D. POLLAK[2,1];
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Abstract: Organisms constantly encounter a wide range of cues in their environment signaling potential threats or rewards. Being able to recognize, interpret, and use those cues to approach potential rewards and avoid potential threats is critical to survival. Indeed, most animals, including humans, are highly adept at learning to associate neutral cues with both rewards and threats. Research with adults has demonstrated that when a neutral cue is paired with a reward or threat three signals of value are encoded neurally: the expected value of the outcome, the value of the actual outcome, and a prediction error (the deviation between actual and expected values). However, the development of these processes and the environmental factors which shape this development are still not well understood. The current work examines how child abuse, which has previously been associated with disrupted value learning, shapes the neurobiological systems responsible for encoding value signals for rewards and punishments. Children 8 - 9 years old (half of whom experienced abuse) were presented with a neutral cue followed by either a reinforcer or a scrambled neutral image. For reinforced trials, the neutral cue was followed by either a reward or punishment. This talk will discuss the psychophysiological mechanisms that modulate children’s ability to learn cue-reinforcer pairings for both rewards and punishments.

Reported results highlight how early life stress exposure affects children's ability to assign value to environmental cues, such as signaling reward or punishment. Given that children who experience abuse early in life demonstrate disrupted social learning across a variety of contexts, this research provides important insight into the neurobiological mechanisms underlying those relationships and informs our understanding of how the early environment shapes the development of value learning and utilization.

Disclosures: K.E. Smith: None. **S.D. Pollak:** None.

Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.05

Topic: A.10. Development and Evolution

Support: NIH Grant HD001106
NIH Grant OD011180

Title: Cortisol in mother's milk predicts head growth and neurological development in the neonatal period in rhesus monkeys

Authors: *A. M. DETTMER[1], J. S. MEYER[2], K. HINDE[3];
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Abstract: Increasing evidence demonstrates a role for bioactives in mother's milk, namely hormones like cortisol, in programming infant biobehavioral development. However, the extent to which such programming occurs in the neonatal period, and thus may influence downstream development, is unclear. We studied 51 socially-housed infant rhesus macaque mother/infant dyads (*Macaca mulatta*, 21 female infants) from birth through postnatal day 30 across four birth cohorts (2013-2016). During routine neonatal neurological assessments modeled closely on the Brazelton neonatal behavioral assessment scale for humans, we collected mother's milk for cortisol analysis (Dettmer et al., 2017) and also conducted infant anthropometric measurements (i.e., head length, biparietal distance [BPD], head circumference; Ruppenthal & Sackett, 1992). Composite scores for neurological assessments were calculated for four domains of development (Schneider et al., 2006): orientation, motor maturity, activity, and state control (a composite of reactivity to the assessment). After controlling for birth cohort, mother's social rank, maternal parity, and infant sex, regression analysis revealed that increases in milk cortisol concentrations across the first month of life (from days 14-30) significantly predicted infant BPD (R^2=0.44,

$p<0.001$) and head length ($R^2=0.54$, $p<0.001$) at day 30. At day 14 higher absolute values of milk cortisol predicted lower motor maturity scores ($R^2=0.34$, $p=0.023$), indicative of lower muscle tonus, coordination, and response speed. Higher milk cortisol at day 30 also tended to predict lower state control scores ($R^2=0.19$, $p=0.068$), indicative of less irritability and easier consolability. These findings are consistent with the "lactational programming" hypothesis and further extend the window for this programming in human and nonhuman primates in the neonatal period, with observable effects just days after birth. Collectively, our results point to a role for hormones in mother's milk, beginning at birth, in neonatal brain growth and neurological and behavioral development. Future studies will be able to draw upon these results to determine the mechanisms for this type of programming.

Disclosures: A.M. Dettmer: None. **J.S. Meyer:** None. **K. Hinde:** None.

Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.06

Topic: A.10. Development and Evolution

Support: NIH R01HD068388
NSF Predoctoral Fellowship
Icahn School of Medicine at Mount Sinai

Title: Synaptic ultrastructure in adolescent rhesus monkeys exposed to sevoflurane in infancy

Authors: *T. FEHR, W. G. M. JANSSEN, M. G. BAXTER;
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Abstract: Several human epidemiological studies have shown an increased risk of learning disability and other behavioral changes following multiple general anesthesia exposures in early life (before the age of 4). Animal studies indicate widespread neural and glial apoptosis from anesthetic exposure early in development, including synapse loss and mitochondrial damage. We have been investigating the behavioral impact of repeated exposure to sevoflurane anesthesia in infant rhesus monkeys, and have found elevated anxiety and impaired visual recognition memory later in life. The long-term impact of anesthesia exposure in infancy on synaptic ultrastructure has not been thoroughly studied. In the present study, we used electron microscopy with unbiased stereological sampling to investigate synapse structure in hippocampal region CA1 in monkeys repeatedly exposed to sevoflurane in infancy, and matched controls, at the age of ~4 years (corresponding approximately to 12 years of age in humans). Rhesus monkeys of both sexes received four-hour exposures to sevoflurane (N=10), or brief maternal separation as a

control (N=10), on postnatal days ~7, 21, and 35. Monkeys were tested in socioemotional and cognitive tasks from 6-48 months of age. We performed electron microscopy targeted in stratum radiatum of area CA1 of the hippocampus. Ultrastructural measures were collected by an experimenter blind to anesthetic condition. There was no difference in synaptic density in CA1 between control and anesthesia groups, but mean synapse area in hippocampal area CA1 was significantly decreased in adolescent monkeys repeatedly exposed to sevoflurane as infants. We conclude that repeated exposure to general anesthesia in infancy can cause changes in ultrastructure of synapses in hippocampal area CA1 that persist (at least) four years, into adolescence. This may relate, in part, to long-term changes in cognition and socioemotional behavior after repeated exposure to general anesthesia in infancy.

Disclosures: T. Fehr: None. **W.G.M. Janssen:** None. **M.G. Baxter:** None.

Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.07

Topic: A.10. Development and Evolution

Support: R01 HD060628
R01 MH091351
K99 MH111805

Title: Maternal nutrition during pregnancy is associated with neonatal functional brain organization and subsequent cognitive skills

Authors: *A. GRAHAM[1], E. SCHIFSKY[1], K. LINDSAY[2], D. STURGEON[1], J. RASMUSSEN[3], E. J. FECZKO[4], S. ENTRINGER[6], P. WADHWA[2], D. A. FAIR[5], C. BUSS[7]; [1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Univ. of California, Irvine, Irvine, CA; [3]Univ. of California, Irvine, Long Beach, CA; [4]Behavioral Neurosci., [5]Oregon Hlth. Sci. Univ., Portland, OR; [6]Charite, Charite, Germany; [7]Charité Univ. Med. Berlin, Berlin, Germany

Abstract: Maternal nutrition and health during pregnancy has important implications for the developing fetal brain. As a prime example, omega-3 fatty acids during pregnancy are essential for fetal neurodevelopment and can only be obtained from the maternal diet. Among the omega-3 fats, docosahexaenoic acid (DHA) is the predominant structural fatty acid in the central nervous system. Animal studies show that maternal DHA during pregnancy facilitates neurogenesis and synaptogenesis in the developing fetal brain and supports emerging cognitive skills. However, the results of human studies are inconclusive. Pregnant women were recruited in early pregnancy and maternal blood samples were collected in each trimester. Non-esterified

(NEFA) DHA was identified by liquid chromatography and mass spectrometry. DHA concentrations across all trimesters were significantly correlated (r=.630 - .677), and a latent variable was created for analyses. Resting state functional connectivity MRI (rs-fcMRI) was collected in neonates during natural sleep (scan age=26.1+/-12.1 days). The hippocampus was segmented using a semiautomatic method, and served as a region of interest for analyses. Infant cognitive development was assessed at 6-months (M=196 days, SD=13.5) with the Bayley Scales of Infant and Toddler Development. Higher maternal DHA during pregnancy was associated with stronger functional connectivity between the neonatal hippocampus and brain regions falling within the default mode network (DMN), cingulo-opercular network (CON) and visual system. Higher maternal DHA was also associated with weaker hippocampal connectivity to the fronto-parietal and somatosensory motor systems. Increased connectivity between the hippocampus and DMN was associated with higher cognitive development scores at 6-months-of-age. Results were consistent after accounting for potential confounds in the pre- and postnatal environment. These results provide evidence in humans to suggest that variation in maternal DHA during pregnancy is associated with differences in functional brain architecture during the neonatal period involving the integration of the hippocampus into large scale brain systems. This may indicate a potential pathway through which maternal dietary DHA can influence cognitive development in humans. This is supported by the association between hippocampal-DMN connectivity and higher cognitive development scores. Ongoing analyses will address how multiple aspects of the prenatal environment, including maternal DHA, other facets of nutrition, and maternal stress levels, relate to neonatal functional brain architecture and emerging cognitive skills.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.08

Topic: A.10. Development and Evolution

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Title: Impact of maternal diet and stressor exposure on lactational programming of infant brain growth: A rhesus macaque study

Authors: *K. ETHUN[1], M. H. KYLE[2], M. PINCUS[1,2], J. GODFREY[1,2], Z. KOVACS-BALINT[1], L. LI[3,2], M. A. STYNER[4], M. E. WILSON[1], M. SANCHEZ[2,1];
[1]Developmental and Cognitive Neurosciences, Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [2]Psychiatry and Behavioral Sci., Emory Univ., Atlanta, GA; [3]Marcus Autism Ctr., Atlanta, GA; [4]Psychiatry and Computer Sci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Breast milk is a complex biofluid comprised of various nutrients and biologically active compounds that can impact infant neurodevelopment and mental health trajectories. Indeed, breastfeeding has been linked to enhanced cognitive and socio-emotional development through early childhood. What is less clear is whether and to what extent postpartum maternal factors such as chronic stress and consumption of an obesogenic diet, both known to alter glucocorticoid signaling and produce a proinflammatory state, influence the programming effects of breast milk on infant brain growth. Because stressor exposure and diet are difficult to manipulate in women, we used social subordination in rhesus macaques as a translational model of chronic stress in women and controlled dietary intake via automated feeders. Starting at birth, forty-one lactating dams (n=21 dominant, n=20 subordinate) were given access to either a low-calorie diet (LCD) only or an obesogenic diet in which both the LCD and a calorically dense diet (CDD) were available *ad libitum.* Brain structural MRI scans were collected on female offspring during early infancy (2wk), late infancy (6mo), and the juvenile pre-pubertal period (16mo), while breast milk was collected during early (2wk), peak (6wk,12wk), and late lactation (6mo). A detailed report of longitudinal effects of diet and stress on brain structural development is provided in M. Kyle et al., at SfN. Here, we present regression analyses indicating a significant relationship between infant brain growth and diet- and stress-induced maternal factors including milk cortisol, proinflammatory cytokine (c-reactive protein, CRP), available milk energy (AME), and milk fat content. Greater AME at peak lactation of mothers fed CDD+LCD predicted larger infant total brain (TBV), prefrontal cortex gray matter (PFC GM), and total insula (INS) volumes at 6mo of age. Higher milk cortisol at peak lactation of mothers fed CDD+LCD also predicted larger TBVs and INS vols. in their infants at 6mo, but not PFC GM vols. Infants of low-ranking mothers fed CDD+LCD had significantly larger amygdala (AMYG) vols. by 6mo of age. These effects were partially explained by increased milk cortisol, CRP, and AME at peak lactation in mothers fed CDD+LCD, particularly among mothers of low social status. Among CDD+LCD-fed mothers, a positive relationship was found between mother's milk yield and infant's TBV and AMYG vols.. However, no relationship was observed between milk fat percent (of total calories) and infant brain size. These findings point to potential mechanisms by which the maternal stress-obesity phenotype impacts breast milk, and in turn, alters infant brain development.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.09

Topic: A.10. Development and Evolution

Support: NIMH F32112232
BBRF NARSAD Young Investigator

Title: Unique neurobehavioral signature of infant trauma with a caregiver

Authors: M. OPENDAK[1], D. A. WILSON[2], *R. M. SULLIVAN[3];
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Abstract: Previous research has identified correlations between early-life trauma and maladaptive outcomes, but the developmental mechanisms initiating the pathway to pathology remain elusive. To better understand how the infant brain responds to trauma and which neurobehavioral responses were causal in initiating the pathway to pathology, we used two complementary rodent models of infant trauma with a caregiver: one naturalistic abuse model and one more controlled, permitting the manipulation of maternal presence during trauma. Our results showed that both procedures produced infant rat pups with similar attenuated neurobehavioral attachment responses to the mother. While maternal presence buffered the effects of acute trauma (shock) on typically-reared pups' amygdala activation, ultrasonic vocalizations, and HPA response, repeated trauma in the presence of the mother led to reversal of these buffering effects and long-term neurobehavioral impairments, including atypical attachment behavior toward the mother. Following trauma with the mother, we observed structural changes in the pup amygdala, including expression of perineuronal nets, parvalbumin contacts on pyramidal cells and the number of immature neurons. We also found that the modulatory strength of the mother had been decreased after five days of abuse: typical maternal caregiving stimuli failed to modulate pups' cortical oscillations and we observed alterations in amgydala dopamine levels and functional connectivity within neural networks responsive to the mother, including the amygdala-VTA circuit. Optogenetic silencing of amygdala during social behavior and blockade of amygdala dopamine during trauma with the mother restored typical attachment behavior, suggesting the amygdala involvement in pup social behavior was atypical. Taken together, these data suggest that the effects of early-life abuse are caused by maternal presence activation of the attachment neural network, combined with trauma to produce

structural and functional changes in the brain. Our work also highlights mesolimbic dopamine as potential novel therapeutic target for infant abuse.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.10

Topic: A.10. Development and Evolution

Support: NIMH Grant U01 MH093349

Title: Intrusive parenting in infancy predicts alterations in error-related theta oscillations seven years later

Authors: *M. BOWERS[1], G. A. BUZZELL[2], S. MORALES[3], A. HANE[4], H. HENDERSON[5], N. FOX[1];
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Abstract: Early parenting behaviors can have a lasting impact on neurocognitive development. In rodent models, presence/absence of the mother has been shown to regulate pups' theta oscillations (4-8Hz) within the mediofrontal cortex. Specifically, mother presence and mother-pup interactions (e.g., grooming, milk ejections) modulate theta during the early postnatal period (Sarro, Wilson, & Sullivan, 2014). In both rodents and humans, mediofrontal event-related theta oscillations integrate information among brain regions to allow for cognitive control. For example, theta power typically increases after errors and relates to changes in task performance (Cavanagh & Frank, 2014), providing an index of cognitive control that can serve as common neural measure to bridge the human and rodent literatures. The goal of this study is to examine for the first time how normal variations in early parenting can affect later error-related theta oscillations in humans. As such, we utilized data from a longitudinal study to investigate relations between parenting behaviors and event-related theta oscillations recorded over mediofrontal cortex (n=291; 156 female). Both sensitive and intrusive parenting were coded at the 9-month assessment in mother-child dyads during routine caregiving tasks (e.g., feeding, changing clothes). At the 7-year assessment, children's error-related theta, an index of cognitive control, was measured by collecting EEG during a go/no-go task. Higher levels of intrusive parenting at 9 months predicted higher mediofrontal theta power on error trials compared to correct trials at age 7 . Critically, only intrusive parenting, not sensitive parenting, was a

significant predictor of error-related theta, suggesting that the effects of parenting on theta is not just due to presence/absence of a parent, but specifically to an intrusive parenting style. Furthermore, this relation held above and beyond any effects of the child's temperament (negative affect, positive affect, and motor reactivity assessed in infancy), suggesting the observed effects on mediofrontal theta are due to parenting rather than child characteristics. In conclusion, early parenting measures, specifically intrusive parenting, impact the development of neural measures of cognitive control.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

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Topic: A.10. Development and Evolution

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Title: Developmental sex heterogeneity of emotion-related brain circuitry in young children

Authors: *J. XU[1,2], L. HAO[1,2], J. GAO[3,4], S. TAN[5], Y. HE[1,2], Q. DONG[1,2], S. TAO[1,2], S. QIN[1,2];
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Abstract: Sex heterogeneity has been recognized in the prevalence of many emotion-related psychiatric disorders, with the rate as twice higher for female than male in depression and anxiety. The etiology of many emotion-related psychiatric disorders emerges during childhood, some of which are substantially sex differentiated. Deciphering developmental sex heterogeneity of emotion processing has important implications for understanding the mechanisms of emotion-related disorders. The amygdala, encompassing a set of interconnected nuclei, the basolateral amygdala (BLA) and centro-medial amygdala (CMA), are two major amygdala nuclei with distinct projections to cortical and subcortical regions, involved in emotion perception,

regulation and expression. Although sex heterogeneity on brain structures and functions were widely documented in adults, little is known about the developmental functional profiles of the amygdala nuclei and their related circuits on different sex. Here we conducted a fMRI study to examine the emotion processing ability in 233 children (aged 7-11 years, Male = 122) and 98 adults (Male = 47). Behaviorally, performance significantly improved with age in girls but not in boys. On the neuroimaging level, we first computed the maturation index to assess the similarity of each child's emotion-related neural activity pattern as relative to the matured brain activity pattern in adults. This analysis revealed that maturation index was significantly positively correlated with age in girls but not in boys. Univariate analyses were conducted to investigate brain systems that exhibit sex heterogeneity from childhood to adulthood. These analyses revealed significant interaction effects on prefrontal cortex and limbic structures like ventral medial prefrontal (vmPFC), CMA and BLA. These regions also showed greater sex heterogeneity in adults compared to children. To further investigate emotion-related circuits, we implemented task-dependent functional connectivity analysis using gPPI. We observed a significant interaction effect on CMA functional coupling with the left insula, with increasing connectivity in male from childhood to adulthood and the opposite pattern in female. We also found a significant interaction effect on BLA functional coupling with the left vmPFC, with decreasing coupling in male but the opposite pattern in female from childhood to adulthood. Together, our findings demonstrated that female matured earlier than male, and delineated the distinct developmental profiles of brain systems involved in emotion processing ability on different sex.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.12

Topic: A.10. Development and Evolution

Title: The effect of prenatal alcohol exposure on offspring brain morphology in childhood and adolescence: A population-based MRI study

Authors: *T. H. SHARP[1], C. RELTON[1], E. WALTON[1], H. EL MARROUN[2], T. PAUS[3], L. ZUCCOLO[1];
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Abstract: The neurodevelopmental consequences of Foetal Alcohol Spectrum Disorder are well characterised, with microcephaly and cognitive deficits consistently reported resulting from heavy prenatal alcohol exposure (PAE). However, there is a significant gap in the literature regarding the impact of PAE in non-clinical populations. Here we describe the results of our exploratory study assessing the association of PAE with brain morphology outcomes during fetal life, childhood, and adolescence.

Data from mother-child pairs were meta-analysed from four population-based cohort studies with a structural MR component. These included; Generation R (*GENR; n=2497 aged 9 years*) in the Netherlands, IMAGEN *(n=1529 aged 14 years*) in Europe, the Saguenay Youth Study (*SYS; n=985 aged 12-18 years*) in Canada, and the Avon Longitudinal Study of Parents and Children (*ALSPAC; n=455 aged 18-21 years*) in the UK. Brain morphology outcomes were defined as global cortical area, mean cortical thickness, and lobar regions of each measure. Fetal trans-cerebellar measures in the 2nd and 3rd trimester were also assessed within GENR. Exposure data were collected prospectively in pregnancy cohorts GENR and ALSPAC, and retrospectively in IMAGEN and SYS. Data were harmonised and PAE measures of timing, intensity and frequency of alcohol use derived. A wide range of covariates relating to the pre and postnatal environment were examined. Our final model adjusted for sex, age and child birthweight, and maternal age, ethnicity, smoking, depression, parity, and socio-economic indicators.

Overall, we found little evidence to suggest PAE is associated with gross morphology alterations in the general population. In our adjusted model, exposed offspring showed a 344.09mm^2 increase in cortical area in GENR (SE 912.97mm^2, p=0.70), 1820.90mm^2 in IMAGEN (SE 1344.99 , p=0.18), -815.40mm^2 in SYS (SE 1711.25, p=0.63) and 398.21mm^2 in ALSPAC, with a pooled estimate of 527.36mm^2 (I^2< 0.00%). When assessing mean thickness, exposed offspring showed a -0.007mm^2 difference in GENR (SE 0.004, p=0.08), 0.023mm^2 in IMAGEN (SE 0.009, p=0.01), -0.006mm^2 in SYS (SE 0.012, p=0.57) and 0.009mm^2 in ALSPAC (SE 0.012, p=0.46), with a pooled estimate of 0.003 (I^2<69.3%). Analyses assessing fetal measures and lobar regions also produced null results when adjusted for multiple testing.

This study will be expanded to incorporate additional neuroimaging data, where increased power will allow detection of smaller effects if present. Causal inference methods, including assessing paternal alcohol consumption as a negative control, and the use of genetic variants to proxy for maternal alcohol use are also underway.

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Nanosymposium

011. Effects of Parenting and Disease on Human and Non-Human Primate Brain Development

Location: Room N427

Time: Saturday, October 19, 2019, 1:00 PM - 4:15 PM

Presentation Number: 011.13

Topic: A.10. Development and Evolution

Support: IARS Grant

Title: Cortical gliosis in juvenile non-human primates exposed to general anesthesia during infancy

Authors: *J. F. PEREZ-ZOGHBI[1], V. NEUDECKER[1], M. R. GRAFE[2], A. M. BRAMBRINK[1];
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Abstract: Introduction: Exposure of infant animals including non-human primates (NHPs) to general anesthetics causes acute brain injury in the developing brain and long-term functional impairment. Within hours of exposure, apoptotic neurons and glial cells become apparent in large numbers. Many types of brain injury including trauma, ischemia, and neurodegenerative conditions like Alzheimer's disease are characterized by chronic glia cell activation (gliosis). Glial fibrillary acidic protein (GFAP) is a cytoskeletal protein in astrocytes that is increased during gliosis and remains elevated for an extended period of time, making it a useful marker of prior brain injury. However, it is unknown whether the brain injury caused by infant anesthesia exposure is also associated with sustained elevated GFAP expression. We hypothesized that GFAP expression is elevated in the brain of juvenile NHPs two years after exposure, indicating long-lasting structural changes following general anesthesia exposure during infancy. **Methods:** Six-day-old NHPs were exposed for 5 hours to isoflurane (ISO) 1.8%, oxygen 30% either one time (1X) or three times (3X) with 72 hours intervals. Control animals were exposed to 30% oxygen. There were 7-8 animals per group with an equal number of males and females. The juvenile animals were euthanized at 2 years of age and the brains fixed and prepared for immunohistology. We assessed changes in GFAP densities in the primary visual cortex (V1), somatosensory cortex, cingulate cortex, and frontal cortex. Slides were digitalized with a Zeiss scanner and the specific brain areas were identified using adjacent sections stained for the neuronal marker NeuN. GFAP density assessments were performed by investigators blinded to the animal group assignment and were unbiasedly quantified by computerized analysis using customized macros in ImageJ. Data are presented as means ± SEM, and ANOVA was used to determine statistical significance between groups. **Results:** GFAP density in the V1 brain area of juvenile NHPs was significantly increased in the 1X exposure group and in the 3X exposure group compared to the control group. GFAP densities in other cortical brain areas are currently being analyzed. **Conclusions:** GFAP density in the visual cortex is increased in juvenile NHPs indicating that cortical gliosis is a new type of long-lasting structural change after anesthesia exposure during infancy. This suggests that GFAP could be a novel histopathological marker of anesthesia-induced injury in the developing brain. GFAP changes may help to identify the anatomical correlates for functional impairments found in juvenile NHPs exposed to general anesthesia as infants.

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Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

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Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.01

Topic: B.07. Synaptic Plasticity

Support: FONDECYT:1161065
CARE-Chile-UC PFB 12/2007
FONDEF D10I1077
CONICYT

Title: c-Abl tyrosine kinase modulates the transcription of immediate early genes in synaptic plasticity

Authors: *D. A. GUTIERREZ[1], D. GONZALEZ[2], A. GONZALEZ[2], P. PICÓN[4], A. CÁCERES[3], F. MUÑOZ[4], *A. R. ALVAREZ[5];
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Abstract: As the synapse matures, receptors like NMDAR and AMPAR accumulate in the membrane of dendritic spines. The activation of these receptors induces the translocation of multiple signals into the nucleus that modulate the expression of immediate early genes (IEG), that later regulate the expression of late-transcription genes contributing to long-lasting neuronal functions and memory. However, the transcriptional regulation of these genes still remain poorly understood. Among several tyrosine kinases that modulate transcription associated with neuronal activity, we focus on the phosphorylation mediated by c-Abl. Here, we describe that after neuronal activity c-Abl is phosphorylated and it localizes into the nucleus. We have found that c-Abl activation depends on the NMDA receptor activation. We also found that c-Abl activity modulates the expression of the IEG, Fosb, Npas4, and Arc. c-Abl knock-out (c-Abl-KO) neurons and neurons treated with c-Abl inhibitors like Imatinib, presented diminished mRNA levels of the IEGs mentioned above after NMDA treatment. We observed a similar trend *in vivo* in models of c-Abl-KO animals challenged in the Morris water maze test.
Key words: immediate early gene, gene regulation, synaptic plasticity, c-Abl tyrosine kinase.

Disclosures: D.A. Gutierrez: None. **D. Gonzalez:** None. **A. Gonzalez:** None. **P. Picón:** None. **F. Muñoz:** None. **A.R. Alvarez:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.02

Topic: B.07. Synaptic Plasticity

Support: BYU Mentoring Environment Grant

Title: True prophylactic treatment effect in a rat PTSD model on synaptic plasticity in ventral hippocampal and lateral amygdala along with potential molecular targets

Authors: *J. G. EDWARDS, R. M. MILLER, E. T. WINZENRIED, E. SAITO, T. JOHNSON, Z. BOYCE, A. MARTIN;
Brigham Young Univ., Provo, UT

Abstract: Post-traumatic stress disorder (PTSD) is a complex disorder that affects about 1 in 4 individuals after a traumatic experience. One common model of PTSD is social defeat (SD) combined with chronic light exposure. First, more naturally anxious rats are determined by results of an open field test where cat fur/fox urine were placed in one quadrant. Rats were classified as anxious if they avoided that quadrant, froze, did not rear, and frequently urinated/defecated. The anxious rats were used in the study. Next, the elevated plus maze (EPM) and light-dark transition (LDT) tests examined anxious behavior at the conclusion of SD. The SD protocol induced significant anxious behavior when compared to controls. Next, we performed long-term potentiation (LTP) field electrophysiology experiments in brain slices of ventral hippocampus (VH) and lateral amygdala (LA), regions known to have altered plasticity in PTSD. SD caused a significant increase in LT) in the VH (~25% greater than control) and LA (~35% greater than control). To determine if a prophylactic treatment could prevent physiological changes of PTSD, propranolol and mifepristone were simultaneously administered (10 mg/kg) by intraperitoneal (IP) injection one week prior and during the entire duration of SD. These drugs significantly decreased LTP in the VH and LA back to near-control levels while SD rats with vehicle injections still had elevated LTP. However, the SD drug treated rats did not show significant reductions in anxious behavior when tested on the EPM and LDT when compared to the SD rats with no drug injections and still exhibited significantly more anxious behavior than control rats, suggesting an IP injection-induced stress as well. Therefore, other forms of drug delivery are currently being examined. Next, gene targets involved in plasticity and stress were examined that may alter the LTP in these cohorts. Significant alterations in the mRNA expression of glucocorticoid, mineralocorticoid, and beta 3 adrenergic receptors; AMPAR, and NMDAR were detected using RT-qPCR between groups in both brain regions. Overall, current data suggest that propranolol and mifepristone together may be a potential prophylactic treatment for preventing PTSD along with some potential molecular targets.

Disclosures: **J.G. Edwards:** None. **R.M. Miller:** None. **E.T. Winzenried:** None. **E. Saito:** None. **T. Johnson:** None. **Z. Boyce:** None. **A. Martin:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.03

Topic: B.07. Synaptic Plasticity

Support: NINDS intramural fund
NIAAA intramural fund
NIBIB intramural fund

Title: Electron microscopy visualization of individual CaMKII molecules at dendritic spines

Authors: *X. CHEN[1], C. WINTERS[1], H. L. PUHL, III[2], V. CROCKER[3], M. ARONOVA[4], R. D. LEAPMAN[4], S. S. VOGEL[2], R. S. THOMAS[1];
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Abstract: CaMKII is the most abundant protein at dendritic spines of excitatory synapses and plays crucial roles in the long term potentiation of synapses. The presence of CaMKII has long been known, but there is no technique available enabling visualization of individual CaMKII molecules in intact synapses. Here we demonstrate our approach by expressing miniSOG or APEX2 tagged CaMKII construct in cultured hippocampal neurons and developing the DAB reaction in the presence of highly viscous sucrose medium which dampens molecular diffusion of the DAB reaction product. We show that, with EM tomography, it is possible to identify individual tagged CaMKII molecules from the three dimensional reconstructions of synapses expressing tagged CaMKII. Our approach opens up the possibility to identify and visualize molecule/complex in intact synapses by EM tomography.

Disclosures: **X. Chen:** None. **C. Winters:** None. **H.L. Puhl:** None. **V. Crocker:** None. **M. Aronova:** None. **R.D. leapman:** None. **S.S. Vogel:** None. **R.S. Thomas:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.04

Topic: B.07. Synaptic Plasticity

Support: NIH Grant K99MH118425
NIH Grant R01MH117139

Title: The role of AMPA receptor C-tails in long-term potentiation

Authors: *J. DÍAZ-ALONSO, S. INCONTRO, R. A. NICOLL;
Cell. and Mol. Pharmacol., UCSF, San Francisco, CA

Abstract: Long-term potentiation (LTP) of excitatory synaptic transmission involves the recruitment of AMPA receptors (AMPARs) to the postsynaptic density (PSD). CaMKII plays a necessary role in this trafficking, but its target(s) remain uncertain. A long held view, referred to as the receptor centric model of LTP, posits that posttranslational modifications in the cytoplasmic C-tail of the AMPAR subunit GluA1 are critical. The modified GluA1-containing receptor is then captured by the PSD. Recent studies from this lab (Granger et al, 2013, Diaz-Alonso et al, 2017) indicate that the receptors are passive players and that CaMKII-induced modification of the PSD creates slots that capture receptors with considerable promiscuity. This is referred to as the PSD centric model of LTP.
A recently generated knockin (KI) mouse, in which the C-tail of the GluA1 subunit has been swapped for the C-tail of GluA2 (referred to as GluA1-A2), lacks LTP. This data has resurrected the receptor centric model and, specifically, the essential role of the C-tail of GluA1 in LTP (Zhou et al, 2018), and appears to be incompatible with the PSD centric model. In order to address this apparent inconsistency, we have carried out four series of experiments: 1) express GluA1-A2 C-tail on an AMPAR null background, 2) express GluA1-A2 C-tail + GluA2(R) on an AMPAR null background, 3) express GluA1-A2 C-tail in cells in which GluA1 has been deleted by CRISPR and 4) generated a KI mouse in which the GluA1 subunit is lacking the C-tail. LTP is normal in the first three sets of experiments. The results from the KI mouse will be presented at the meeting.

Disclosures: J. Díaz-Alonso: None. **S. Incontro:** None. **R.A. Nicoll:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.05

Topic: B.07. Synaptic Plasticity

Support: R01NS053978

Title: Rab27b regulates frequency facilitation and is essential for long-term potentiation in hippocampal mossy fiber synapses

Authors: *E. R. ARIAS-HERVERT[1], **N. XU**[1], E. L. STUENKEL[2];
[1]Mol. & Integrative Physiol., [2]Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Neurotransmitter exocytosis from presynaptic terminals involves synaptic vesicle (SV) targeting to; docking and priming at the active zones; and Ca^{2+}-triggered membrane fusion. The transitions between docking and priming steps are stochastic and reversible, and greatly influence the dynamics of vesicle fusion. In hippocampal neurons, Rab3a and Rab27b control SV docking and priming steps by interacting with effectors expressed at the active zones. The effect of these Rab-GTPases on the synaptic transmission is only evident after the ready-releasable pool (RRP) has been depleted by repeated stimulation at moderate frequencies. In Rab3a knockout mice, synaptic depression in SC-CA1 synapses is enhanced, while LTP is selectively blocked in Mf-CA3 synapses. On the other hand, previous data from our lab showed that Rab27b knockout significantly reduces synaptic depression in SC-CA1 synapses in response to 14 Hz stimulation, but to our knowledge, it is not known whether Rab27b is required for Mf LTP in Mf-CA3 synapses. Therefore, the aim of this work was to characterize the synaptic properties of Mf-CA3 synapses in hippocampal slices of Rab27b knockout and wild type mice, using field recordings and engineered Lentiviral particles to manipulate protein expression. The data presented here show strong effects of Rab27b knockout on synaptic transmission in Mf-CA3 synapses. Comparison of input-output functions revealed a significant 1.6-fold increase in the slope in mutant mice compared to wild type (n: WT=8, KO=7, *P=0.03); on the other hand, paired-pulse ratio evaluated at 40 ms was not significantly different between WT and KO (n=12, P=0.14), but frequency facilitation was 50% reduced in mutant mice (n=12, *P=0.007); and Mf LTP was completely lost (n=6). These effects were accompanied by a significant reduction in Tomosyn 1 (n=3, *P=0.02), a putative Rab-GTPase effector involved in the regulation of synaptic plasticity. Finally, expression of human Rab27b in mutant mice rescued the Rab27b knockout phenotype, demonstrating Rab27b specificity. Together, these data show that Rab27b negatively regulates frequency facilitation and is essential for expression of LTP in Mf-CA3 synapses.

Disclosures: E.R. Arias-Hervert: None. **N. Xu:** None. **E.L. Stuenkel:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.06

Topic: B.06. Synaptic Transmission

Support: R37 MH052804
K99 MH103531

Title: Alternative splicing of presynaptic neurexins differentially controls postsynaptic NMDA and AMPA receptor responses

Authors: *J. DAI[1], J. N. AOTO[2], T. C. SUDHOF[1];
[1]Stanford Univ., Stanford, CA; [2]Pharmacol., Univ. of Colorado, Denver, Aurora, CO

Abstract: AMPA- and NMDA-type glutamate receptors mediate distinct postsynaptic signals that differ characteristically among synapses. How postsynaptic AMPA- and NMDA-receptor levels are regulated, however, remains unclear. Using newly generated conditional knockin mice that enable genetic control of neurexin alternative splicing, we show that in hippocampal synapses, alternative splicing of presynaptic neurexin-1 at splice site 4 (SS4) dramatically enhanced postsynaptic NMDA-, but not AMPA-receptor-mediated, synaptic responses without altering synapse density. In contrast, alternative splicing of neurexin-3 at SS4 suppressed AMPA-, but not NMDA-receptor-mediated, synaptic responses, while alternative splicing of neurexin-2 at SS4 had no effect on NMDA- or AMPA- receptor-mediated responses. Presynaptic overexpression of the neurexin-1b and neurexin-3b SS4+ splice variants, but not of their SS4 splice variants, replicated the respective SS4+ knockin phenotypes. Thus, different neurexins perform distinct nonoverlapping functions at hippocampal synapses that are independently regulated by alternative splicing. These functions transsynaptically control NMDA and AMPA receptors, thereby mediating presynaptic control of postsynaptic responses.

Disclosures: J. Dai: None. **J.N. Aoto:** None. **T.C. Sudhof:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.07

Topic: B.06. Synaptic Transmission

Support: NINDS Intramural Funds

Title: From presynaptic terminal to postsynaptic spine: Trans-synaptic bridges within hippocampal synapses revealed by EM tomography

Authors: *A. A. COLE, X. CHEN, T. S. REESE;
NINDS - Lab. of Neurobio., NIH, Bethesda, MD

Abstract: In dissecting the molecular machines that contribute to synaptic function, compartments are typically considered independent. Recent light-level evidence indicates

possible alignment between presynaptic release sites and postsynaptic receptors in hippocampal synapses. Here, we traced the transmembrane material associated with trans-cleft filaments in electron tomograms and revealed contiguous trans-synaptic bridges between complex protein assemblies in the pre- and postsynaptic compartments. The EM tomographic reconstructions were made of synapses in three-week-old dissociated mouse hippocampal cultures prepared for EM tomography by high-pressure freezing and freeze-substitution. Electron dense objects of interest were segmented by adjusting a threshold seeded in a 3D ROI around each object. Only those trans-cleft filaments with trans-membrane and intra-cellular structure on each side of the synapse were included in renderings. Presynaptic structures associated with trans-synaptic bridges manifest as flat masses along the membrane or as bulky complexes with vertical extensions. In the postsynaptic compartment, trans-synaptic bridges associate with small masses that lay along the membrane or bulky complexes, distinct from those found in the presynaptic compartment. In some cases, postsynaptic vertical filaments extend from bulky complexes and connect to filaments horizontal to the synaptic membrane, possibly the MAGUK scaffolding of the postsynaptic density and pallium. Along the periphery of the synapse, a small subset of trans-synaptic columns associate with flat material laying along the membrane in both intra-cellular compartments. Some docked synaptic vesicles connect to filaments associated with bridges and align with bulky complexes in the postsynaptic compartment. These observations paint a new picture of connections between elements in the synapse and illustrates how two neurons might collaboratively organize protein distribution for optimized transmission. Future work will focus on differentiating bridge types by structure and sorting out their functions. The resolution of EM tomography makes it a great tool for investigating columnar alignment of synaptic receptors, vesicles, and trans-synaptic bridges.

Disclosures: **A.A. Cole:** None. **X. Chen:** None. **T.S. Reese:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.08

Topic: B.06. Synaptic Transmission

Support: NIH F31 NS103365

Title: *In vivo* genetic analysis of dendritic spine morphogenesis and postsynaptic assembly

Authors: *D. OLIVER[1], A. PHILBROOK[1], S. RAMACHANDRAN[1], K. C. Q. NGUYEN[2], D. H. HALL[2], M. DOITSIDOU[3], C. BÉNARD[4], M. M. FRANCIS[1];
[1]Univ. of Massachusetts Med. Sch., Worcester, MA; [2]Albert Einstein Col. Med., Bronx, NY; [3]The Univ. of Edinburgh, Edinburgh, United Kingdom; [4]Univ. du Québec à Montréal, Montréal, QC, Canada

Abstract: Morphogenesis and plasticity of dendritic spines are crucial for proper neural circuit function, and disruptions in these processes have been implicated in numerous neurological disorders. Mammalian models have shed light on a variety of cellular processes driving spine extension and the formation of postsynaptic specializations, but gaining a complete understanding of the specific molecular contributions of these processes *in vivo* remains an ongoing challenge. Recently, our lab discovered that a subset of excitatory synapses in the nematode *Caenorhabditis elegans* are located on finger-like protrusions from GABAergic dendrites. This was surprising because *C. elegans* synapses between nerve processes occur *en passant*, and dendritic spines had not been previously implicated. Using light and electron microscopy, we demonstrate that these structures share key characteristics with mammalian dendritic spines: (1) they are apposed by synaptic vesicle clusters, (2) are decorated with clusters of neurotransmitter receptors, (3) are highly enriched in F-actin, (4) can be categorized into distinct classes based on morphological features, and (5) grow in number and length during development. This newly defined *C. elegans* dendritic spine model permits an in-depth, step-by-step analysis of dendritic spine formation *in vivo* using the genetic tools and synaptic markers available in this system. We are now investigating the progression of molecular events underlying the development of nascent synapses at single spine resolution. Towards this end, we carried out a forward genetic screen to identify required genes, and, to date, have isolated key molecules from 3 gene classes, including kinesin binding proteins, neurotransmitter receptor subunits, and synaptic scaffolds. We are now investigating the specific functions of these gene products in spines. Our work offers a novel and complementary genetic system to explore the machinery and mechanisms driving spine outgrowth and synapse assembly *in vivo*.

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Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.09

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS079419
NIH Grant NS101832

Title: Activity labeling reveals electrophysiological differences between L4 pyramidal neurons with high and low *in vivo* firing rate set points

Authors: *N. TROJANOWSKI, G. TURRIGIANO;
Dept of Biol., Brandeis Univ., Waltham, MA

Abstract: Excitatory neurons in visual cortex (V1) display remarkably stable firing rates over many days, even though for each neuron these baseline rates can vary over many orders of magnitude. In response to prolonged sensory perturbation, firing rates of individual neurons transiently drop but eventually homeostatically return to their baseline firing rate. Thus, these neurons have individual firing rate set points. Little is known about the factors that determine these set points, or how neurons within a single cell type but with disparate set points might differ electrophysiologically, morphologically, or transcriptionally. To better understand the mechanisms that neurons within a single cell type use to maintain divergent baseline activity levels *in vivo* we used CaMPARI2, a fluorescent protein that undergoes Ca^{2+}- and UV-dependent photoconversion, to permanently label excitatory neurons in V1 based on their baseline activity in freely behaving mice. We illuminated a CaMPARI2-expressing region of V1 for 30 minutes with a UV LED coupled to a fiberoptic cannula, and found that the ratio of converted (red) to un-converted (green) CaMPARI2 correlated well with the firing rates of neurons in an active slice preparation. This suggests that the CaMPARI2 photoconversion ratio is a good marker of *in vivo* activity. We then used this activity label to compare electrophysiological properties between nearby high and low activity neurons. In layer 4 (L4) star pyramidal neurons, which comprise a single transcriptional cell type, we found multiple differences between high and low activity neurons. High activity neurons had a right-shifted F-I curve, a lower rheobase current, and decreased spike adaptation index relative to low activity neurons, revealing an increased intrinsic excitability. Surprisingly, we found no difference in total excitatory or inhibitory charge or in E/I ratio between high and low activity neurons. Thus, within a single cell type differences in intrinsic excitability and spike frequency adaptation can contribute to divergent baseline activity levels. In contrast to L4 pyramidal neurons, in L5 non-bursting pyramidal neurons we found no differences in intrinsic excitability between low and high activity neurons, suggesting that the mechanisms used to maintain distinct activity set points may vary by cell type. These results demonstrate that activity labeling via CaMPARI2 enables us to uncover electrophysiological differences between neurons of the same cell type with high and low activity, which provides a first step towards understanding how neurons within a single cell type can develop and maintain divergent firing rate set points.

Disclosures: N. Trojanowski: None. **G. Turrigiano:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.10

Topic: B.07. Synaptic Plasticity

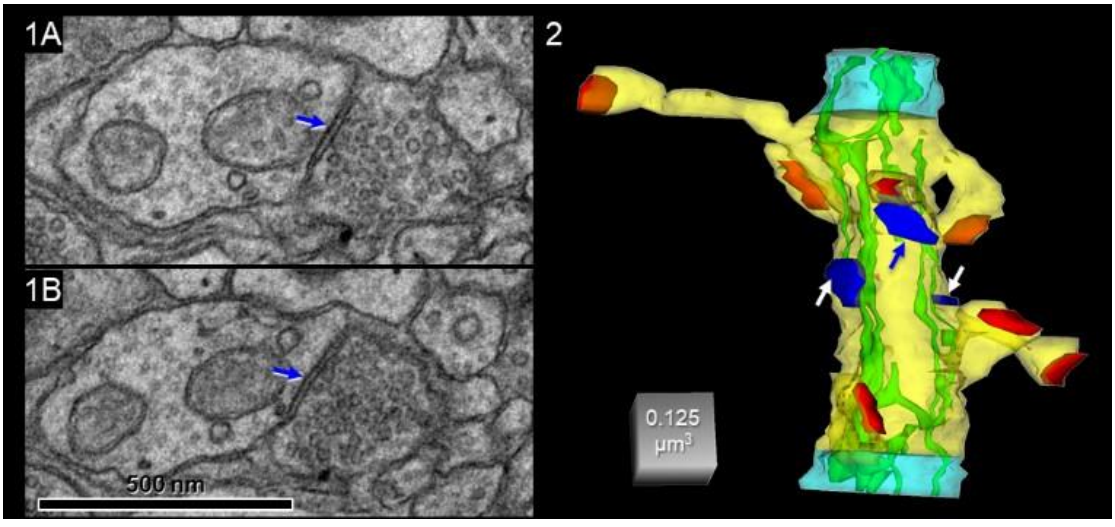
Support: NIH Grant 1R01MH104319-01A1,02,03,04,05
NSF Grant 1707356

NIH Grant 2R56MH095980-06

Title: Effects of inhibitory synapses on dendritic spine clustering in rat hippocampus

Authors: *K. M. HARRIS, M. M. HOOPER, D. D. HUBBARD, Z. A. LUNA, J. M. MENDENHALL, P. H. PARKER, J. N. BOURNE, M. A. CHIRILLO;
Dept. of Neurosci. and Ctr. for Learning and Memory, Univ. of Texas at Austin, Austin, TX

Abstract: The goal of this study is to determine whether inhibitory synapses influence the frequency or size of dendritic spines in a cluster. Symmetric, presumably inhibitory synapses were characterized by presynaptic axonal boutons filled with pleiomorphic vesicles and equally thin pre- and postsynaptic densities (Fig. 1, blue arrows). As illustrated in Fig. 2, synaptic clusters (yellow) were delineated by surrounding non-synaptic regions at least 120 nm in length (light blue, average 250 nm); asymmetric, presumably excitatory synapses (red) are distinguished from the symmetric synapses (royal blue, blue and white arrows); and the smooth endoplasmic reticulum (green) was also reconstructed. Two stimulating electrodes were positioned with a separation greater than 600 microns surrounding a recording electrode in the middle of CA1 stratum radiatum in two hippocampal slices from different young adult rats. Theta-burst stimulation (TBS) was given to one electrode and produced saturated LTP that was monitored for 2 hours with test pulses (at a rate of 1 per 2 minutes). The other stimulating electrode (control) delivered the same number of test pulses but no TBS. Preliminary analyses from 136 synaptic clusters across the LTP and control conditions show that fewer synaptic clusters ($X^2 = 5.9$, p=0.015) contained symmetric synapses at 2 hours after LTP (0.07±0.03/µm) than after control stimulation (0.31±0.1/µm, ANOVA, $F_{(1,132)}=7$, p=0.0096). The surface areas of the symmetric synapses were larger in the LTP (0.18±0.0 µm^2) than the control condition (0.084±0.03 µm^2, ANOVA, $F_{(1, 21)}=5$, p=0.0096). Overall, synaptic clusters with inhibitory synapses had lower dendritic spine density (4.23±0.64 spines/µm) than those without inhibitory synapses (6.7±0.41 spines/µm, ANOVA, $F_{(1, 132)}=8.6$, p=0.004). In contrast, synaptic clusters with inhibitory synapses had comparable spine densities in the LTP (4.04 ±0.69 spines/µm) and control (4.32±0.65 spines/µm) conditions. These results suggest that the presence of inhibitory synapses can influence local spine density and plasticity.



Disclosures: **K.M. Harris:** None. **M.M. Hooper:** None. **D.D. Hubbard:** None. **Z.A. Luna:** None. **J.M. Mendenhall:** None. **P.H. Parker:** None. **J.N. Bourne:** None. **M.A. Chirillo:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.11

Topic: B.07. Synaptic Plasticity

Support: ERC-AdG 787450
German Research Foundation (FOR2143)

Title: Spine dynamics in parvalbumin-positive interneurons of the dentate gyrus upon environmental changes

Authors: D. KAUFHOLD, E. MARISTANY, M. STRÜBER, J. SAUER, *M. BARTOS;
Inst. for Physiol. I, Univ. Freiburg, Freiburg, Germany

Abstract: Dendritic spines of principal cells form electrical and biochemical compartments as critical sites of synaptic transmission. They can undergo dynamic modifications in their structure as well as changes in signalling efficiency, which have been considered to be key elements of memory formation. Some interneuron types such as somatostatin-positive cells are known to possess spines, whereas others, such as parvalbumin-expressing interneurons (PVIs), have been considered to be spineless. In contrast to this prevailing view, recent studies indicate that PVIs may possess spines. Moreover, PVIs undergo behaviour-dependent changes in protein expression and synaptic plasticity at their glutamatergic inputs, suggesting that PVIs may undergo functional and structural changes. Thus, here we examined structurally dynamics of dentate gyrus (DG) PVIs. We stereotactically injected adeno-associated viruses carrying a GFP reading frame inverted in a flip-excision cassette into the hippocampus of PV-Cre mice. (1) We performed detailed morphological analysis of PVIs and show that a subpopulation of DG-PVIs is spiny (~50%; 0.15 spines/µm). (2) PVIs in CA1/3 are not spiny. (3) PVIs with somata at the hilus-granule cell layer border show higher spine densities than those in the granule cell or molecular layer. (4) Spine densities are higher in the dorsal DG (dDG). (5) Electron microscopy reveals that spines receive putative asymmetric glutamatergic synaptic inputs, which are functional and contain AMPA and NMDA receptors as proved by *in vitro* 2-Photon Ca^{2+}-imaging in combination with glutamate uncaging. (6) Mice exposed to an enriched environment show changes in density and distribution of PVI spines in an afferent-specific manner. (7) Single unit recordings of mice exposed to a new environment show enhanced activity of optogenetically identified PVIs. Thus, our data indicate that dendritic spines of PVIs undergo structural modifications upon environmental changes, which may have profound effects on local connectivity and microcircuit computation.

Disclosures: **D. Kaufhold:** None. **M. Bartos:** None. **E. Maristany:** None. **J. Sauer:** None. **M. Strüber:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.12

Topic: B.07. Synaptic Plasticity

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
NIH R01 NS081281

Title: Toward the identification of a mechanism that controls GABAergic synapse density

Authors: *R. KOHEN[1], K. T. BALDWIN[2], P. M. GARAY[1], A. CHEN[1], C. G. FLYNN[3], M. A. SUTTON[4], S. IWASE[5], R. J. GIGER[6];
[1]Neurosci. Grad. Program, [2]Cell. and Mol. Biol. Program, [3]Sch. of Kinesiology, [4]Mol. and Integrative Physiol., [5]Human Genet., [6]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, MI

Abstract: CNS inhibitors block neurite outgrowth *in vitro* and contribute to the growth-restrictive environment of the injured adult mammalian brain and spinal cord in vivo. In the naïve brain, NogoA is expressed by neurons and oligodendrocytes, functioning as a negative regulator of structural plasticity and activity-dependent synaptic strength. In primary hippocampal neurons, prolonged changes in neuronal network activity regulate NogoA surface expression in a bidirectional manner: in the presence of TTX, surface NogoA decreases, whereas bicuculline treatment increases surface NogoA. To assess whether acute depletion of neuronal NogoA in hippocampal neurons influences homeostatic synaptic plasticity, we used two independent approaches: (1) Lentiviral Vector (LV)-mediated shRNA knockdown, and (2) LV-Cre recombinase-mediated deletion in *Nogo*$^{flox/flox}$ cultures. Both methods resulted in robust loss of NogoA expression. Biochemical analysis of LV-shRNA transduced cultures revealed a striking reduction in presynaptic markers for GABAergic synapses. Immunofluorescence staining independently confirmed the strong reduction in inhibitory synapses. However, a similar reduction in synaptic proteins was not observed in LV-Cre transduced *Nogo*$^{flox/flox}$ cultures. Since Cre recombination results in deletion of all Nogo isoforms (Nogo-A/-B/-C), and LV-shRNA leads to selective knockdown of NogoA, we explored Nogo isoform-specific effects. Strikingly, LV-shRNA transduction of *Nogo*$^{flox/flox}$ cultures, with or without prior infection with LV-Cre, mimics the strong synaptic phenotypes observed in LV-shRNA-infected wildtype cultures. This suggests involvement of NogoA-independent factors. To assess off-target effects of LV-shRNA, we subjected hippocampal neurons infected with either control LV-GFP or LV-shRNA to RNA-sequencing, whereby investigating nascent and stable changes in transcription. Consistent with

biochemical studies, LV-shRNA leads to significant changes in transcripts associated with inhibitory synaptogenesis. The top hit of downregulated genes was NogoA by a large margin, providing confidence in the shRNA's primary target. To distinguish between gene products regulated by Nogo-A/-B/-C deletion and LV-shRNA knockdown, we are currently carrying out comprehensive sequencing experiments with *Nogo*$^{flox/flox}$ cultures infected with LV-Cre, with or without LV-shRNA. Intersectional analysis of these data sets is expected to provide mechanistic insights into the regulation of synapse formation and composition.

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Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.13

Topic: B.03. G-Protein Coupled Receptors

Support: HHMI
Sackler Scholar Fellowship

Title: Plasticity of dopamine and PKA dynamics in the striatum during reward based learning

Authors: *S. LEE[1], Y. CHEN[1], T. PATRIARCHI[2], L. TIAN[2], B. SABATINI[1];
[1]Neurobio., Howard Hughes Med. Inst. - Harvard Med., Boston, MA; [2]Dept. of Biochem. and Mol. Med., Univ. of California Davis, Davis, CA

Abstract: A circuit involving the midbrain dopamine (DA) neurons and the striatum has been proposed as a central circuit for reward based learning. Previously, many groups have reported that the DA neurons encode a reward prediction error (RPE), which can provide a learning signal for the downstream circuit such as the striatum. While these studies have provided with a fundamental model of a circuit capable of learning, there are still missing links in this model. First, does the somatic activity of DA neurons that encodes RPE drive the release of DA in the striatum during reward based learning? Because the release of DA by DA neuron terminals can be manipulated by both somatic action potentials and striatal local inputs onto the DA neuron terminals, the relationship between the DA neurons' somatic activity and the DA level in the striatum remains unclear. To investigate this question, we performed the dual-color/dual fiber photometry with a genetically encoded calcium indicator and an optical DA sensor for mice undergoing a visual cue guided operant conditioning with food rewards. Our data shows a progressive change in a Ventral Tegmental Area (VTA) DA neuron cell body Ca^{2+} signal, a VTA DA neuron terminal Ca^{2+} signal in the nucleus accumbens (NAc), and a DA release pattern in the NAc that are highly correlated. Second, what is the striatal neurons' intracellular substrate for

DA and basal ganglia dependent learning process? Previously, the PKA pathway has been proposed to be central to basal ganglia-dependent motivational learning because it can be regulated by DA receptors in striatal neurons. However, testing of this hypothesis has been limited by the difficulty of directly observing the activity of an intracellular pathway in behaving animals. To overcome this limitation, we performed fluorescence lifetime measurements with fiber photometry to monitor endogenous PKA activity in neurons in freely behaving animals. Employing this technology to monitor PKA activity as well as a conventional fluorescence intensity fiber photometry technique to monitor a DA level, we examined the relationship between DA release and PKA activity in the NAc during reward-based learning.

Disclosures: S. Lee: None. **Y. Chen:** None. **T. Patriarchi:** None. **L. Tian:** None. **B. Sabatini:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.14

Topic: B.03. G-Protein Coupled Receptors

Support: Howard Hughes Medical Institute
NINDS R37NS046579
Nancy Lurie Marks Foundation

Title: Can protein kinase inhibitor peptide (PKI) act as a switch between kinases?

Authors: *Y. CHEN[1], B. L. SABATINI[2];
[1]Neurosci., Washington Univ., Saint Louis, MO; [2]Neurobio., Howard Hughes Med. Institute, Harvard Med. Sch. Dept. of Neurobio., Boston, MA

Abstract: Protein kinase A (PKA) integrates diverse neuromodulator and neurotransmitter inputs and exerts important effects on synaptic transmission, synaptic plasticity, and transcription. An important regulator of PKA activity is protein kinase inhibitor peptide (PKI). PKI is an endogenous peptide that binds to the catalytic subunit of PKA to inhibit PKA function. In addition, PKI has been extensively used as a pharmaceutical agent to inhibit PKA to isolate PKA specific effect in neurobiology. Despite its extensive usage, the specificity of PKI to PKA was not well characterized. We have screened PKI against a panel of kinases to examine the specificity of PKI, and will report our results in this presentation.

Disclosures: Y. Chen: None. **B.L. Sabatini:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.15

Topic: B.06. Synaptic Transmission

Support: National Natural Science Foundation of China (31800856)
Shanghai Pujiang Program (18PJ1402600)

Title: Stress hormone induces synaptic plasticity of the ventral tegmental area dopamine neurons via D2 receptor signaling

Authors: B. PENG[1], S. GUO[2], S. L. BORGLAND[2], ***S. LIU**[1];
[1]East China Normal Univ., Shanghai, China; [2]Univ. of Calgary, Calgary, AB, Canada

Abstract: Ventral Tegmental Area (VTA) is a critical site for reward seeking as well as stress response. Dysregulation of VTA has long been implicated in stress-related disorders. However, the mechanism by which stress hormone alters neuroplasticity in VTA dopamine neurons is largely unknown. In the present study, we treated mice with either vehicle or corticosterone (CORT) in the drinking water to study the effect of CORT on VTA dopamine neurons and stress related behaviors. 7d CORT treatment induced anxiety and depression like behaviors, as well as decreased risky food approach behaviors. By using whole cell patch clamp, we show decreased excitability of VTA dopamine neurons in CORT mice. Excitatory and inhibitory synaptic transmission onto the VTA dopamine neurons were both decreased in CORT treated mice. Paired pulse ratio confirmed decreased release probability at excitatory synapses, with no change in the AMPAR/NMDAR ratio in VTA dopamine neurons of CORT mice. No significant difference was observed in the endocannabinoid tone. Fast scan cyclic voltammetry tests revealed increased somatodendritic dopamine in the VTA. D2R antagonist sulpiride restored decreased excitatory transmission and excitability of VTA DA neurons in CORT mice. Taken together, CORT treatment, as used for anti-inflammatory and asthma treatments, can have profound influences the function of the mesolimbic dopamine system via D2 receptor signaling and can influence risk taking behaviors.

Disclosures: B. Peng: None. **S. Guo:** None. **S.L. Borgland:** None. **S. Liu:** None.

Nanosymposium

012. Neural Excitability: Regulating Synaptic Properties and Plasticity

Location: Room N426

Time: Saturday, October 19, 2019, 1:00 PM - 5:00 PM

Presentation Number: 012.16

Topic: B.07. Synaptic Plasticity

Support: NIH Grant

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

Authors: L. N. FRIEND[1], ***B. WU**[2], J. G. EDWARDS[2];
[1]NIH, North Bethesda, MD; [2]Brigham Young Univ., Provo, UT

Abstract: The ventral tegmental area (VTA) in the midbrain modulates reward processing. Drugs of abuse can increase midbrain dopamine (DA) activity, and can alter VTA 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 (LTD) of glutamatergic inputs onto VTA GABA neurons. Δ9- tetrahydrocannabinol, the active ingredient in marijuana and CB1 agonist, initiates LTD at this synapse with acute slice application, and occludes this plasticity following chronic (7-10 days) 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/GFP-positive 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 after a single cocaine injection to the naïve state, as LTD was again observed following 7 days of abstinence. Furthermore, chronic cocaine application decreased AMPA/NMDA ratios (0.82 cocaine; 1.1 saline), compared to vehicle-only injections, which importantly is the opposite of the cocaine-induced change in the ratios at glutamatergic inputs to VTA DA cells. Collectively, cocaine's decrease in AMPA receptors could depress excitability of VTA GABA cells and its altering of plasticity could mediate some of cocaine's addictive effects via GABA cells in addition to cocaine-induced changes of VTA GABA cells.

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

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.01

Topic: B.11. Glial Mechanisms

Support: EU Horizon 2020 under the Marie Skłodowska-Curie grant agreement No 665385 for G.C.
DOC Fellowship of the Austrian Academy of Sciences at the IST Austria for R.S.

European Research Council (ERC), grant agreement No. 715571 for S.S.

Title: Topological classification of microglia

Authors: G. COLOMBO[1], ***A. VENTURINO**[1], R. SCHULZ[1], L. KANARI[2], K. HESS[3], S. SIEGERT[1];
[1]IST Austria, Klosterneuburg, Austria; [2]EPFL, Blue Brain Project, Geneve, Switzerland; [3]EPFL, Lausanne, Switzerland

Abstract: The structure and the shape of a neuron determines its physiological function. In the retina, for example, we can predict on the spatial disposition of ganglion cell dendrites whether they respond to light on and off. Microglia exist in different morphological states during development, adulthood, and degeneration across various brain regions. We still lack knowledge how to categorize microglia in a meaningful way and to identify potential sub-clusters of microglial population based on their morphology. Previous attempts have used one or few morphometrics such as total filament length, number of Sholl intersections etc. to extract morphological features to distinguish population. This feature selection however biases the classification because the statistical feature choice deeply influences the outcome and reduces reproducibility.
Topology can overcome these limitations, and has been already successfully applied to classify cortical neurons. Here, we generated a morphological atlas of microglia from brain regions associated with various diseases during development and degeneration. Then, we generated 3D-skeleton of over 20.000 microglial filament structures and mathematical assessed the filaments using a topological descriptor. The generated persistence images allow us to quantify the diversity of microglia morphology across brain regions, their changes during development and degeneration, as well as the difference between sexes. First, we investigated microglia differences across brain regions in adulthood. Then, we focused on how much the identified populations differ between development and degeneration. Our analysis confirms the influence of spatial location, age and health condition on microglial cells morphology. We can now categorize microglia in defined clusters in an unbiased way.
Our database will provide an important tool to investigate the correlation between microglia morphology and functional state as well as provide a platform to describe the microglial functional state within the scientific community. Our goal is to implement a searchable database that will allow the end-user to compare their microglia morphology under a defined experimental condition to our pre-defined clusters.

Disclosures: G. Colombo: None. **A. Venturino:** None. **R. Schulz:** None. **L. Kanari:** None. **K. Hess:** None. **S. Siegert:** None.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.02

Topic: B.11. Glial Mechanisms

Support: SFARI #346197
NIH #P50MH112491
Rettsyndrome.org #3214
Stanley Center for Psychiatric Illness at the Broad Institute

Title: Uncovering functional roles for unique microglia subpopulations in development and disease

Authors: *T. R. HAMMOND[1], C. DUFORT[2], A. YOUNG[4], E. DEERHAKE[5], M. SHINOHARA[5], B. A. STEVENS[3];
[1]Kirby Neurobio., [3]Harvard Med. Sch. Neurobio., [2]Boston Children's Hosp., Boston, MA; [4]Cambridge Univ., Cambridge, United Kingdom; [5]Duke Univ., Durham, NC

Abstract: Microglia, the tissue resident macrophages of the central nervous system, are necessary for normal brain development and respond rapidly to brain pathology. Our recent data suggest that microglia are highly diverse in development and disease, raising the question about the functional role of these subpopulations in different contexts. Our single cell genomic analysis uncovered distinct transcriptional signatures that we are now using to develop tools to track and manipulate different microglia states. Unique microglia subpopulations include neonatal axon tract associated microglia in developing axon tracts and inflammatory microglia in mouse models of Multiple Sclerosis and neurodegenerative disease, We use loss of function and cell depletion approaches to understand the function of each subpopulation and to test the role of immune signaling and microglia-neural interactions on normal brain development and recovery from pathological insult.

Disclosures: T.R. Hammond: None. **C. Dufort:** None. **A. Young:** None. **B.A. Stevens:** None. **M. Shinohara:** None. **E. Deerhake:** None.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.03

Topic: B.11. Glial Mechanisms

Support: OSU Graduate Fellowship
OSU Startup Funds

Title: Microglia support developmental cell genesis and myelination

Authors: *L. H. NELSON[1], P. PEKETI[2], S. WARDEN[2], B. VEROSKY[2], H. HICKEY[2], F. ZHAO[3], C. ASKWITH[3], K. M. LENZ[4,5];
[1]Neurosci. Grad. Program, [3]Dept. of Neurosci., [4]Psychology, [5]Inst. for Behavioral Med. Res., [2]Ohio State Univ., Columbus, OH

Abstract: Microglia, the resident macrophages of the CNS, support synaptogenesis, synaptic pruning, cell proliferation, myelination, and sexual differentiation during development (Nelson & Lenz, 2017). We have previously shown that reversibly depleting microglia from the neonatal rat brain, using central infusion of liposomal clodronate, decreased anxiety, behavioral despair, and the acute stress response in adulthood (Nelson et al., 2017). Microglia may be programming behavior by supporting myelination as myelin is needed for proper neural connectivity. Myelination is consistently altered in psychiatric disorders and may be a novel way to treat psychiatric disorders (Haroutunian et al., 2014). To determine whether microglia support myelination, we infused liposomal clodronate (2μL icv; Encapsula Nanoscience) in male and female rats on postnatal days (P) 1 and 4, which temporarily depletes 90% of forebrain microglia. We assessed the gene expression of two major myelin proteins, myelin basic protein (Mbp) and proteolipid protein-1 (Plp1), in the prefrontal cortex and amygdala at P14 and P21. These brain areas were chosen based on their involvement in the behavioral changes we found in our previous study, and the etiology of psychiatric disorders. Relative to controls, Mbp and Plp1 were decreased at P12 in the amygdala and medial prefrontal cortex, but only decreased in the amygdala at P21. Similar to Mbp gene expression, Mbp labeling in the central and basolateral amygdala at P21 in clodronate treated rats. Lastly, the anterior commissure and corpus callosum width were decreased relative to controls at P21. Myelination deficits are apparent after microglia recolonization thus the myelination deficit may be due to decreased production of oligodendrocytes earlier in development, at the time of microglia depletion. Previously, we found decreased cell genesis on P3 in the amygdala, motor cortex, hippocampus, and corpus callosum after microglia depletion. We currently hypothesize that decreased oligodendrocyte progenitor cell (OPC) proliferation and production of oligodendrocytes drives the decrease in cell genesis. We are now investigating oligodendrocyte proliferation the prefrontal cortex, amygdala, and corpus callosum at P7. Preliminary results suggest that microglia depletion decreased the number of OPCs and proliferating OPCs, but did not change the number of oligodendrocytes. Future work will determine if myelin deficits last until adulthood, and whether there are any functional changes in white matter tracks. Thus, microglia may contribute to the developmental component of psychiatric disorders via regulation of myelination.

Disclosures: L.H. Nelson: None. **P. Peketi:** None. **S. Warden:** None. **B. Verosky:** None. **H. Hickey:** None. **K.M. Lenz:** None.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.04

Topic: B.11. Glial Mechanisms

Support: Wellcome Trust PhD Grant
BJA/NIAA

Title: Microglia mediate restructuring of spinal somatosensory circuits during normal development and after injury

Authors: *Y. XU[1], D. MOULDING[2], O. GIBBS[3], S. BEGGS[1,2];
[1]Neuroscience, Physiol. and Pharmacol., [2]Great Ormond Street Inst. of Child Hlth., [3]Univ. Col. London, London, United Kingdom

Abstract: Maturation of sensory systems is an activity-dependent process and requires modality specific input in early postnatal life. Spinal somatosensory circuits are functional at birth but undergo extensive postnatal reorganization, with refinement of afferent input and maturation of inhibitory circuits.

Peripheral tissue injury during this period of maturation (1st postnatal week in rodents) results in long-term changes in local and whole-body pain sensitivity, which can be prevented by pharmacological inhibition of spinal microglial activity at the time of injury. Since microglia are known to refine neural circuits through selective strengthening or elimination of synapses in normal brain development, we hypothesized that 1) microglia refine spinal somatosensory/ nociceptive circuits during normal postnatal development through pruning, and 2) tissue injury during that period disrupts microglial pruning, thus altering circuit refinement and subsequent pain behavior.

To test these hypotheses, we have mapped postnatal changes in microglial density, phagocytic activity, and complement production in the spinal dorsal horn using immunostaining in wildtype and transgenic reporter mice. Further, we have determined microglial interaction with local synapses and peripheral afferent input in normal development and after postnatal hind paw incision injury.

During normal development, microglial phagocytic activity is highest during the 1st postnatal week, with phagocytic cup numbers and microglial lysosomes decreasing after P7. Over the same period, peripheral afferent fibers are engulfed by microglia throughout the dorsal horn, decreasing after P10. Together this data supports the hypothesis that microglia refine afferent projection during 1st postnatal week through pruning.

Early postnatal hind paw incision induces microglial proliferation in the ipsilateral dorsal horn, increases microglial lysosome numbers, as well as phagocytosis of afferent projection fibers in males, but did not affect microglial contact with local synapses in both sexes.

Genetic disruption of microglial phagocytosis and *in-vivo* electrophysiological studies are currently underway to determine whether microglial pruning is critical for the development of dorsal horn sensory function.

Our results suggest a microglia-mediated refinement of afferent projections in the dorsal horn through phagocytosis and potential dysregulation of that process after early postnatal injury,

which may underly subsequent pain sensitization. An understanding of this process will improve preventative pain management.

Disclosures: **Y. Xu:** None. **D. Moulding:** None. **O. Gibbs:** None. **S. Beggs:** None.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.05

Topic: B.11. Glial Mechanisms

Support: NIMH (P50MH094271)

Title: Bcl-xL gene imprinting regulates neuron-specific microglia crosstalk and cortical plasticity

Authors: *M. D. CAIATI, O. HO-SHING, C. G. DULAC, T. K. HENSCH;
Harvard Univ., Cambridge, MA

Abstract: Beyond its well-established function in cell death, the apoptotic pathway may regulate neuronal synaptic transmission and plasticity under physiological conditions. Moreover, it has been implicated in the regulation of the immune complement cascade at the synaptic level. Whether and how active caspases might play a role in synapse development and cell-specific neuro-immune crosstalk (in the absence of ongoing cell-death) is unknown. Here, we examined Bcl-xL, an anti-apoptotic factor expressed widely in the post-mitotic neocortex, which is imprinted throughout the mouse brain - exhibiting a robust paternal expression bias. In the visual cortex, we find this parent-of-origin allelic expression of Bcl-xL impacts synapse maturation, plasticity and microglia-neuronal coupling. Using *in vitro* patch-clamp recordings combined with biocytin filling and *post hoc* neuronal 3D-reconstrution, we observed that paternal (but not maternal) Bcl-xL deletion halted the maturation of AMPA-mediated excitatory synaptic transmission. It also prevented long-term potentiation (LTP) and blocked the visual experience-dependent pruning of dendritic spines specifically in Satb2+ callosally projecting pyramidal neurons. These phenotypes were rescued by inhibitors of caspase 3. Consistent with this, the highly quantitative single molecule FISH method unveiled monoallelic *Bcl-xL* expression specifically in Satb2+ neurons. In contrast, we found that *Bcl-xL* expression was biallelic in microglia, the resident immune cells of the brain. Accordingly, both maternal and paternal deletion affected microglia, as revealed by flow cytometric, morphological and gene expression analyses. Altogether, our study reveals a surprising parent-of-origin and cell-type specific role for Bcl-xL in cortical maturation and experience-dependent plasticity. More broadly, our data reveal new insights into the involvement of the apoptotic pathway in microglia-neuronal

coupling with cell-specific implications for the imprinted regulation of proper cortical development.

Disclosures: **M.D. Caiati:** None. **O. Ho-Shing:** None. **C.G. Dulac:** None. **T.K. Hensch:** None.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.06

Topic: B.11. Glial Mechanisms

Support: WPI-IRCN (JSPS)

Title: Enhanced parvalbumin neuron-microglia crosstalk during critical period plasticity

Authors: ***H. H. LEE**[1], K. B. QUAST[2], M. D. CAIATI[2], R. K. REH[1], N. W. HODGSON[1], M. NAKAMURA[2], J. SPATAZZA[3], A. PROCHIANTZ[3], T. K. HENSCH[1,2,4];
[1]FM Kirby Neurobio. Program, Boston Children's Hosp., Boston, MA; [2]Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [3]Col. De France, Paris, France; [4]Intl. Res. Ctr. for Neurointelligence, Univ. of Tokyo, Tokyo, Japan

Abstract: Parvalbumin (PV) circuits control the timing of critical periods (CP) in primary visual cortex (V1). Here, we directly examined downstream consequences of their maturational state. Fast-spiking properties of PV-cells gradually emerge with CP onset and can be reset by adult depletion of the non-cell autonomous factor, Otx2. Microarray and qPCR analyses of FACS-sorted cortical cells revealed bidirectional PV cell-specific changes in the complement (C1q) system when Otx2 was, respectively, increased in the pre-CP or depleted later in adulthood. This suggested a role for microglia in regulating CP plasticity. Indeed, the rapid loss of thalamocortical synaptic input onto PV-cells by monocular deprivation was abolished by microglial blockade. Likewise, the parallel, rapid induction of oscillatory rhythms in the γ frequency range (30-80 Hz) *in vivo* was attenuated by microglial blockers. To delve deeper into the relationship of γ oscillations and microglial activation, we examined a conditional mouse model lacking GABA(A) α1 receptor subunits only in PV-cells (PV-α1 KO mice). This genetic manipulation persistently enhances γ-power and extends cortical plasticity beyond the normal CP across the neocortex. These mice displayed elevated complement gene expression and an increased number of activated microglia in the cortex. In addition, both the impaired perineuronal nets (PNN) and extended cortical plasticity in adult PV-α1 KO mice were reversibly rescued by microglial inhibitors. Taken together, microglia and the complement system might enable CP plasticity by reflecting PV-network plasticity and function. Understanding neuro-immune interactions on local PV-circuit physiology during the CP may

yield novel therapeutic strategies for neurodevelopmental disorders, including autism, major depression and schizophrenia.

Disclosures: H.H. Lee: None. **K.B. Quast:** None. **M.D. Caiati:** None. **R.K. Reh:** None. **N.W. Hodgson:** None. **M. Nakamura:** None. **J. Spatazza:** None. **A. Prochiantz:** None. **T.K. Hensch:** None.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.07

Topic: B.11. Glial Mechanisms

Title: Functional and molecular characterization of a human iPSC-derived microglial model

Authors: *T. A. LANZ[1], M. SHEEHAN[2], Q. XIAO[3], M. ZAVODSKY[2], R. CHALLA[2], H. MCLAUGHLIN[2], C. SUN[2], C. ROBERTS[2], H.-H. TSAO[3], S. ENGLE[2], R. KLEIMAN[2]; [1]Investigative Toxicology, Pfizer, Groton, CT; [2]Translational Biol., [3]MSRU, Biogen, Cambridge, MA

Abstract: Microglia play critical roles in normal brain development and have attracted attention for potentially pathologic roles in a number of neurologic and psychiatric disorders. We established a previously published protocol (Haenseler et al., Stem Cell Reports 2017) for developing a human iPSC-derived microglia model and performed extensive molecular and functional characterization. Continuously produced microglial mature over the course of a week in culture, after which time they are immunoreactive for Iba1, display ramified morphology, show active engulfment of myelin debris, and secrete inflammatory cytokines in response to LPS stimulation. The RNAseq profile of these iPSC microglia were compared to a published dataset from acutely isolated microglia (ex vivo) from human brain and the same cells maintained in primary culture for 7-10 days (in vitro). While the iPSC derived microglia showed many differences from the ex vivo microglia, they were very similar to the in vitro human microglia. iPSC microglia were then co-cultured with iPSC cortical neurons to provide more biological cues for development. Single-cell RNAseq profiling identified a distinct sub-population of iPSC microglia in the co-culture condition that was not present when only microglia were present. This distinct microglial cluster was characterized by reduced expression of genes involved in cell proliferation and metabolic pathways, and enrichment for IFN signaling and a number of genes associated with ex vivo microglia. These changes are consistent with a more mature microglial phenotype following the addition of human neurons to the cellular environment. The presence of microglia did not alter the RNA profile of the cortical neurons. Balancing model complexity with adaptability for screening will be important for enabling such translatable human cellular models to advance drug discovery efforts.

Disclosures: **T.A. Lanz:** A. Employment/Salary (full or part-time):; Biogen. **M. Sheehan:** A. Employment/Salary (full or part-time):; Biogen. **Q. Xiao:** A. Employment/Salary (full or part-time):; Biogen. **M. Zavodsky:** A. Employment/Salary (full or part-time):; Biogen. **R. Challa:** A. Employment/Salary (full or part-time):; Biogen. **H. McLaughlin:** A. Employment/Salary (full or part-time):; Biogen. **C. Sun:** A. Employment/Salary (full or part-time):; Biogen. **C. Roberts:** A. Employment/Salary (full or part-time):; Biogen. **H. Tsao:** A. Employment/Salary (full or part-time):; Biogen. **S. Engle:** A. Employment/Salary (full or part-time):; Biogen. **R. Kleiman:** A. Employment/Salary (full or part-time):; Biogen.

Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

Time: Saturday, October 19, 2019, 1:00 PM - 3:15 PM

Presentation Number: 013.08

Topic: B.11. Glial Mechanisms

Support: FONDECYT Grant 1171434 (JE)
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CONICYT 3180553 (SBC)
DICYT-USACH (JE)

Title: CO_2-sensitive microglia in mouse brainstem

Authors: *J. E. EUGENIN[1], E. IRRIBARRA[1], S. BELTRÁN-CASTILLO[2], C. DANIELA[1], A. FLORES[1], R. VON BERNHARDI[2];
[1]Univ. de Santiago, USACH, Santiago, Chile; [2]Pontificia U Catolica De Chile, Fac Med., Santiago, Chile

Abstract: Central chemoreceptors contribute to the adaptation of breathing to physiological demands. Neurons and astrocytes, located in respiratory chemosensitive nuclei, release neurotransmitters and gliotransmitters in response to increases in CO_2 and H^+. Microglia, the resident immune cells of the CNS, through their surveillance, are able to detect different extracellular signals, which depending on their nature, can trigger an integrative microglial response to maintain brain homeostasis. Since microglia are in constant dialogue with neurons and astrocytes, we evaluate here whether brainstem microglia modify their phenotype when neurons and astrocytes are activated by hypercapnic acidosis. Adult CF1 mice were exposed to air enriched with 10% CO_2 for 30 min followed by inhalation of pure air for 60 min. Control mice were exposed only to pure air for 90 min. Mice were anaesthetized, their brains extracted, fixed and processed for immunohistochemistry against Iba-1, a microglia marker. We found that prolonged hypercapnia modified the shape of the brainstem microglia in chemosensory nuclei such as the NTS, raphe and ventral respiratory column (VRC). The size of their cell bodies increased and the number of their primary branches were reduced by hypercapnia. By contrast,

the phenotype of microglia from hippocampus, neocortex, and the spinal trigeminal nucleus were unmodified by hypercapnia. In addition to the morphological changes, the expression of CD86, a M1 phenotype marker, increased in microglia exposed to hypercapnia. By contrast, CD206, a M2 phenotype marker, maintained its low level of expression. Similar changes were also observed in pure cultures of microglia exposed to hypercapnia. In these cultures, we also detected by ELISA, the increase in the release of IL-1β, but not of TGF-β. Our results show that microglia are sensitive to prolonged hypercapnia acquiring a pro-inflammatory phenotype. Whether this activation is enhanced by the activation of neurons or astrocytes is an open question.

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Nanosymposium

013. Microglial Control of Brain Development and Function

Location: Room S106

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Presentation Number: 013.09

Topic: B.11. Glial Mechanisms

Support: 1F99NS108486-01

Title: *In vivo* imaging of microglial self-renewal and maturation in the adult mouse brain

Authors: ***M. S. MENDES**[1], J. ATLAS[1], Z. BREHM[2], M. MCCALL[2], A. K. MAJEWSKA[1]; [1]Neurosci., Univ. of Rochester Med. Ctr., Rochester, NY; [2]Dept. of Biostatistics, Univ. of Rochester, Rochester, NY

Abstract: Microglia are the resident macrophages of the brain. They are long-lived and have been implicated in neurodevelopmental and neurodegenerative diseases. Therefore, it is important to understand how these cells rearrange, renew and mature because disruptions of microglia can induce permanent changes in their immune response. However, the mechanisms and the kinetics by which microglia renew and acquire mature characteristics in the adult brain are not entirely understood. To explore this, we used PLX5622 to deplete microglia and chronic *in vivo* two-photon imaging in the visual cortex of awake adult $CX_3CR1^{GFP/+}$mice to longitudinally track microglial repopulation and maturation. Under basal conditions, microglial self-renewal is a slow and stochastic process. During depletion, there is a shift to rapid and regional microglial loss. With repopulation, microglia are rapidly replaced from existing microglia *in vivo*. We observed two subpopulations of microglial cells: one that is continuously and rapidly renewing through the splitting of somata and another that is quiescent and long-lived but migrates spatially. To understand whether the microglial proliferation (splitting of somata) could account for the rapid replacement of microglial cell numbers, we imaged microglia every 2

hours for 24 hours at the peak time for microglial proliferation. Characterization of the doublets during this time revealed one population of doublets cells that split off after only 4 hours and a second population that remained a doublet for >12 hours. In some cases, we observed a secondary division of the newly generated cells. Mathematical modeling of our imaging data showed that the local proliferation of existing microglia accounts for the increase in microglial cell numbers during repopulation, suggesting that repopulation is carried out locally within each brain area, rather than from special populations that are spatially restricted. Additionally, both newly-generated and surviving microglia adopted ramified morphologies and resumed surveillance of the brain rapidly (within a few days) after PLX5622 treatment was discontinued. However, quantitative sholl analysis showed that newly-born microglia where hyper-ramified compared to controls. In addition, we observed that newly-born microglia respond robustly to acute laser ablation injury. Taken together our work suggests that newly-born microglia rapidly mature morphologically, but exhibit altered properties that may affect their ability to carry out their supportive roles in the brain.

Disclosures: **M.S. Mendes:** None. **J. Atlas:** None. **Z. Brehm:** None. **M. McCall:** None. **A.K. Majewska:** None.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

Time: Saturday, October 19, 2019, 1:00 PM - 4:00 PM

Presentation Number: 014.01

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

Support: NIH Grant R37 AG008796 (Disterhoft)
NIH Grant R01 AG061787 (Savas)

Title: Brain proteome changes associated with aging, cognitive decline, and cognitive superaging

Authors: *C. B. SPÄNI, M. M. OH, A. DISTAULO, M. MCCARTHY, N. KHALATYAN, J. N. SAVAS, J. F. DISTERHOFT;
Northwestern Univ., Chicago, IL

Abstract: Aging has a negative impact on cognition across multiple species. Especially forms of learning that require an intact hippocampal formation are severely impacted in aged humans, mice, and rats. However, some individuals seem to escape this age-related cognitive decline. These cognitively-unimpaired “superagers” are capable of learning and remembering at the same levels as young individuals even at advanced ages. This study is designed to investigate brain proteome changes during aging, and changes associated with cognitive status, i.e. what changes

in protein levels are associated with cognitive impairment and superaging respectively.
We behaviorally characterized F344 rats (both sexes) at various ages using trace eyeblink conditioning (TEBC) and Morris water maze (MWM). Based on the results of both tests, animals were characterized as either cognitively impaired or unimpaired. One month after the last training session, animals were killed, and brains dissected into seven different regions (cerebellum, CA1, CA3, dentate gyrus, and prefrontal, entorhinal, and visual cortex). Those brain regions were then analyzed using state-of-the-art mass spectrometry (MS)-based proteomics to determine global protein changes.
Our preliminary results show proteomic brain changes occurring during normal aging and associated with cognitive status. For example, comparing aged (20-23 months) to middle-aged (12-14 months) male entorhinal cortex samples (n=5) shows approximately 200 significantly up or down-regulated proteins, with monoglyceride lipase, Ras-related protein Rag-4B, and annexin being the most significantly changed. Interestingly, the PANTHER pathway analysis revealed the blood coagulation pathway was significantly enriched in the aged animals suggesting a potential link between blood circulation and aging in the brain.
The results of this study are important to understand the underlying mechanisms of cognitive aging and will hopefully lead to new ideas and intervention/prevention targets for successful cognitive aging. Further, we will use the same experimental approach to compare brain proteome changes in a rat model of Alzheimer's Disease (AD) to those of unsuccessful aging and superaging.

Disclosures: C.B. Späni: None. **M.M. Oh:** None. **A. DiStaulo:** None. **M. McCarthy:** None. **N. Khalatyan:** None. **J.N. Savas:** None. **J.F. Disterhoft:** None.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

Time: Saturday, October 19, 2019, 1:00 PM - 4:00 PM

Presentation Number: 014.02

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

Support: NIA Grant AG061846-01

Title: Detection of aberrant protein folding in neurodegenerative diseases with covalent protein painting

Authors: *T. C. BAMBERGER, J. DIEDRICH, J. R. YATES, III;
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Abstract: A common denominator of several different neurodegenerative diseases is the appearance and accumulation of misfolded proteins. The aggregation of specific proteoforms like

amyloid-β $A\beta_{1-40}$ in Alzheimer's disease (AD) has been pinpointed to cause neurodegeneration. However, it remains unclear whether a proteome-wide altered protein folding landscape determines the molecular pathology during onset and progression in late onset Alzheimer disease. This question remains open mainly because a quantification of protein conformation and protein-protein interactions is still missing on a proteome wide scale.
To address this need we developed a bottom-up mass spectrometry based proteomic approach to scan a proteome for aberrant protein folds and protein-protein interactions at low spatial resolution but with high throughput. "Covalent Protein Painting" (CPP) exploits the selective chemical reactivity of lysine residues when solvent exposed and quantifies it so that changes in reactivity are revealed quantitatively. In CPP altered chemical reactivity serves as a proxy to measure altered protein conformation or interaction.
We applied CPP to human brain samples of patients with Alzheimer disease that are characterized by aggregation of tau and Aβ. CPP surveyed 4522 lysine sites in 1069 protein groups and detected a distinct inaccessibility of 10% to 30% lysine K28 of Aβ in AD patient samples in support of fibrillar aggregated Aβ. Few additional proteins showed altered chemical reactivity in AD samples in comparison to controls. We determined whether newly identified, conformationally altered proteins differed between patients with disease with Lewy Body (DLB) and AD and found that protein conformation analysis of the heat shock protein HSP90 might specifically distinguish DLB patient samples from AD(only) patient samples. A conformational alternation of the endoplasmic reticulum chaperone BiP (HSP5A, GRP78) differentiated AD(only) samples from both, DLB and controls. In summary, we show that proteome-wide analysis of protein conformation and interaction with CPP identifies conformationally altered proteins potentially involved in neurodegenerative diseases. The results may point to altered protein folding landscapes that might distinguish late onset neurodegeneration.

Disclosures: **T.C. Bamberger:** None. **J. Diedrich:** None. **J.R. Yates:** None.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

Time: Saturday, October 19, 2019, 1:00 PM - 4:00 PM

Presentation Number: 014.03

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

Support: UCI Start Up Funds
American federation for Aging Research Young Investigator Award

Title: Single-cell transcriptome identifies conserved transcriptomic alterations in Alzheimer's disease

Authors: S. J. MORABITO[1], E. MIYOSHI[2], N. MICHAEL[3], ***V. SWARUP**[3];
[1]Grad. Program in Mathematical, Computat. and Systems Biology., [2]Interdepartmental Neurosci. Program, [3]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Large scale data-driven analyses of the human brain across various neurodegenerative diseases possess the potential for identifying disease-specific biological processes. Alzheimer's disease (AD) is a devastating neurodegenerative disease, characterized by changes in cell-type proportions and marked alterations of the transcriptome. We used a data-driven integrative genomics approach across multiple human AD cohorts and integrated single-cell transcriptomes from postmortem human brain to identify key transcriptional changes. We examined both the coding and the non-coding transcriptome and unraveled conserved transcriptional changes across hundreds of human AD samples. Co-expression network analysis identified robust dysregulation of the transcriptome in AD that was not found in normal human aging. Co-expression changes across multiple brain regions reflect selective regional vulnerability and identify the temporal cortex as the site associated with the earliest and largest gene expression changes. Using single-nuclei RNA-seq we profiled 29,321 nuclei from normal human cortex and unambiguously defined robust neuronal and non-neuronal subtypes based on the single-cell transcriptional profiles. By leveraging the single-cell clusters, we developed a framework to assess cell-type proportion changes in the human AD brain. We also found that genetic variants of AD are enriched in glial-associated AD modules and identified key transcription factors regulating these modules. Finally, we validated our findings in multiple published human AD datasets and show that our findings identify robust and reproducible transcriptomic alterations of the diseased brain.

Disclosures: S.J. Morabito: None. **E. Miyoshi:** None. **N. Michael:** None. **V. Swarup:** None.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

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Presentation Number: 014.04

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

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NIA 1R01AG057911 to CG
NIA 1R01AG061798 to CG

Title: Multi-omic analysis identifies transcriptional networks and drivers associated with cognitive aging and Alzheimer's disease

Authors: *S. E. HEUER[1,3], S. M. NEUNER[1,4], C. GAITERI[5], C. C. KACZOROWSKI[2]; [2]Genomics, [1]The Jackson Lab., Bar Harbor, ME; [3]Sackler Sch. of Grad. Biomed. Sci., Tufts Univ., Boston, MA; [4]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [5]Rush Alzheimer's Dis. Ctr., Rush Univ. Med. Ctr., Chicago, IL

Abstract: It is well known that genetics play an important role in determining risk for developing Alzheimer's disease (AD). The goal of this study was to use a mouse genetic reference panel to identify the genetic factors that influence cell-type composition and transcriptional networks mediating individual differences in cognitive decline. We assessed working memory and contextual fear memory in a genetically diverse population of mice harboring familial AD mutations (AD-BXDs) and their non-transgenic littermates (Ntg-BXDs), at either 6 or 14 months of age, and built gene co-expression modules from hippocampal RNA-sequencing data collected at 6 or 14 months. To identify transcriptional networks and driver genes that explain variation in cognitive outcomes, we calculated Pearson correlations between module expression and cognitive measures, and identified 15 significantly correlated modules. A number of these modules were modified by AD mutations, including two immune-enriched modules that most significantly associated with variance in contextual fear acquisition and memory. The top module associated with working memory variance was enriched for pathways related to cellular protection from oxidation. Genetic mapping of this module highlighted a locus on chromosome 6 containing a novel putative driver of module expression and working memory outcomes. Finally, we used Bayesian modeling to integrate genetic, genomic, and cognitive scales of data in order to prioritize several causal module-trait relationships for future interrogation. Overall, this model provides new insights into the upstream genetic and genomic processes regulating cognitive outcomes during aging and AD. Work incorporating brain-wide cell-type maps seeks to identify modules associated with variance in numbers of neurons, astrocytes, and microglia across multiple brain regions in the AD- and Ntg-BXD panel, which will help elucidate the cellular mechanisms that influence transcriptional networks that underlie aging- and AD-related cognitive outcomes. In addition, we observed a high degree of conservation between mouse and human ROS/MAP modules, highlighting the translatability of our mouse panel for use in discovery-based research and candidate validation that is likely to inform treatment of human AD.

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Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

Time: Saturday, October 19, 2019, 1:00 PM - 4:00 PM

Presentation Number: 014.05

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

Title: Transcriptomic analysis of the brain endothelium in an experimental model of Alzheimer's disease

Authors: *A. JANA[1], A. JAMBUSARIA[2], H. B. DODIYA[5], J. LEASURE[3], S. SISODIA[5], J. REHMAN[4];
[1]Med., [2]Bioengineering, Pharmacol., [3]Pharmacol., [4]Medicine, Pharmacology, Bioengineering, Univ. of Illinois at Chicago, Chicago, IL; [5]Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Background: Blood brain barrier (BBB) dysfunction is associated with Alzheimer's disease (AD) but the mechanisms by which BBB dysfunction affects AD progression are not fully established. Brain endothelial cells (ECs) are key components of the BBB and recent studies point towards a mechanistic role for endothelial dysfunction in the development and progression of AD. To understand the mechanisms by which brain ECs may affect AD progression, we used an unbiased transcriptomic analysis approach to analyze gene expression in brain endothelial cells derived from the transgenic mouse line (APP/PS1DE9) that expresses familial AD-linked Amyloid Precursor Protein (APPswe) and presenilin 1 (PS1ΔE9) in all CNS cell types, leading to deposition of Aβ peptides in plaques.
Methods: RNA-seq was used to analyze the transcriptional profiles of ECs isolated from forebrain of young (~4 months) and old (~13 months) transgenic AD (APP)/presenilin (PS1DE9) mice as well as age matched non-transgenic control mice (strain C3H/BL6). For EC isolation, mice were perfused with ice cold PBS and forebrains were dissociated with collagenase /dispase and DNAse. After myelin depletion, ECs were enriched by using CD31 microbeads and the purity of the ECs was verified by flow cytometry. RNA-Seq analysis was performed on the EC mRNA and PCA plots as well as pathway analysis was used to identify gene expression pathways that were selectively upregulated or downregulated in AD mice versus their age-matched controls.
Results: PCA plots demonstrated that brain EC samples from old AD mice (n=5) clustered together and were most distinct from the gene expression profiles of brain ECs derived from young control mice (n=5). Old control mice (n=5) and young AD mice (n=5) exhibited an intermediate phenotype. We therefore focused the analysis on comparing old AD mice to old control mice. Old AD brain ECs were characterized by downregulation of genes involved in neurotransmitter transport, synaptic organization and axon development when compared to old control brain ECs. On the other hand, old AD brain ECs showed upregulation of inflammatory pathways such as responses to type 1 interferon signaling the regulation of cell adhesion.
Conclusions: The signature patterns of gene expression changes in brain endothelial cells of aged transgenic AD mice suggest a significant shift in the endothelial function suggestive of endothelial
inflammation as well as the intriguing finding that brain ECs may downregulate cues important for axon function and synaptic transport as AD progresses. Mechanistic interventions on selected genes in these pathways could establish the novel causal roles of these processes in AD.

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Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

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Presentation Number: 014.06

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

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Title: Insight into alpha1ACT transcription factor interactome in cerebellar development and degeneration

Authors: C. WEI, D. P. H. PASTOR, J. GODFREY, E. RAO, C. GOMEZ, ***X. DU**; Neurol., Univ. of Chicago, Chicago, IL

Abstract: The α1ACT transcription factor is crucial for regulating cerebellar development and function. We have previously shown that loss of α1ACT in early life causes developmental delay, while expression of α1ACT with expanded polyglutamine (polyQ) tract ($\alpha1ACT_{SCA6}$) leads to Purkinje cell degeneration and spinocerebellar ataxia type 6 (SCA6) in adults. Identification of the proteins which interact with α1ACT and $\alpha1ACT_{SCA6}$ may clarify the molecular and cellular pathways involved in α1ACT/$\alpha1ACT_{SCA6}$ transcriptional regulation and SCA6 pathogenesis. Here we utilized an unbiased proteomic approach to identify proteins which interact with either wild type or polyQ-expanded α1ACT.We also implemented RNAseq to explore the transcriptional profiles of the wild type and polyQ-expanded α1ACT. Using overexpressed flag-tagged wild type or polyQ-expanded α1ACT as bait, we identified binding proteins through flag pull-down purification and subsequent LC-MS/MS analysis. By clustering the functional annotations of the identified proteins, we identified distinct Gene Ontology (GO) terms betweenwild type and polyQ-expanded α1ACT. Both wild type and polyQ-expanded α1ACT were shown to interact with proteins involved with intracellular protein transport and cellular localization as well as transcriptional regulating protein, suggesting their involvement in the nucleo-cytoplasmic transport of α1ACT/$\alpha1ACT_{SCA6}$and gene regulation by α1ACT.Using RNA-seq weshowed that wild type and polyQ-expanded α1ACThave distinct transcriptional profiles. While the α1ACTdataset was enriched in mRNAs associated with dendrite morphogenesis and signal release, those for polyQ-expanded $\alpha1ACT_{SCA6}$were enriched with mRNAs associated with neuron death and DNA damage. Our results help to elucidate the mechanistic differences between α1ACT loss and expression of polyQ-expanded α1ACT and helps to delineate between the disparate diseases associated with each. We show that polyQ-

expanded α1ACT interacts with different proteins than wild type does and that it has distinct transcriptional gene targets. This study also provides an insight to identify potential therapeutic targetsfor treating developmental delayand neurodegenerative disorders.

Disclosures: C. Wei: None. **D.P.H. Pastor:** None. **J. Godfrey:** None. **E. Rao:** None. **C. Gomez:** None. **X. Du:** None.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

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Presentation Number: 014.07

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

Support: F31 AG059364
R01 AG061787

Title: Determining and characterizing substrates of impaired protein degradation in models of Alzheimer's disease

Authors: *T. J. HARK, E. BOMBA, S. N. SMUKOWSKI, L. ALI, J. N. SAVAS; Northwestern Univ., Chicago, IL

Abstract: Alzheimer’s disease (AD) is the most prominent neurodegenerative disorder, affecting over 40 million people worldwide. Behaviorally, symptoms of AD include a decline in short-term memory and deteriorating executive functioning. Molecularly, the hallmarks of AD include misfolded and aggregated plaques and tangles, consisting of amyloid beta 1-42 peptides ($A\beta_{42}$) and hyperphosphorylated tau, respectively. $A\beta_{42}$ accumulation is one of the earliest pathological events; however, how $A\beta_{42}$ induces toxicity in neurons and contributes to synaptic dysfunction remains poorly understood. One hypothesis is that $A\beta_{42}$ hampers protein degradation causing vulnerable proteins to abnormally linger in the brain. My project aims to determine the specific proteins that have decreased degradation dynamics in mouse models of AD-like pathology, and subsequently explore why these proteins persist. In order to investigate which proteins’ degradation is stunted due to AD-like pathology, I utilize pulse-chase stable isotope labeling in mammals (pcSILAM) with the recently developed APP knock-in mice (APPKI) followed by proteomic-based quantitative mass spectrometry (MS). APPKI mice endogenously express humanized APP with mutations common to familial AD, recapitulating AD-like pathology. PcSILAM-MS enables unbiased quantification of thousands of proteins by tracking the pulsed isotopes following a chase period, thus allowing me to determine which proteins have protracted lifetimes following AD-like pathology. I found that the proteins persisting in pathogenic mice compared with non-pathogenic controls were significantly enriched for proteins associated with

the presynapse. These proteins had impaired degradation in the cortex and hippocampus, but not the cerebellum, where $A\beta_{42}$ pathology only occurs at late stages of disease progression, supporting an $A\beta_{42}$ dependent effect. I am now using biochemical assays and microscopy to investigate why these presynaptic proteins persist in response to AD-like pathology. Preliminary data suggests that these proteins and possibly whole presynaptic terminals are nearby or associated with plaques. Together, these experiments suggest presynaptic proteins are among the earliest perturbed in AD-like pathology potentially due to their close association with $A\beta_{42}$'s processing, release, and aggregation. These perturbed proteins and protein networks may critically contribute to mechanisms of early AD pathology and further inform our understanding of this debilitating disease.

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Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

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

Support: Royal Society Grant RSG\R1\180118
University Alliance DTA3 COFUND Grant

Title: Cellular mechanisms in memory retrieval and its impairment in amyloid precursor protein transgenic mice, as revealed by synapse proteomics

Authors: *V. BEGLOPOULOS, A. J. RHODES, D. BECIC, A. C. ASHTON;
Sch. of Pharm. and Biomed. Sci., Univ. of Central Lancashire, Preston, United Kingdom

Abstract: While the process of formation of new memories is extensively studied, there are still many questions unanswered regarding the mechanisms underlying memory retrieval. Our previous work in a mouse model has suggested that memory retrieval might be the first component of memory deteriorating in the early stages of Alzheimer’s disease (AD), and demonstrated an increase in memory retrieval-associated brain glucose uptake in WT mice, but not in amyloid precursor protein transgenic (APPtg) mice (Beglopoulos et al., 2016, Nat Commun). While these data have implications for earlier diagnosis and biomarker development, investigation of the associated cellular events could shed light on the mechanisms underlying memory retrieval and possibly contribute to our further understanding of memory loss in early AD. This study, which has both confirmatory and exploratory elements, aims to a) test our hypothesis of stimulus-dependent mitochondrial transport to synapses as a mechanism

underlying memory retrieval and its impairment in APPtg mice, and b) identify additional candidate cellular pathways. Using J20 APPtg and WT mice, two behavioral groups were analysed: a) a memory retrieval group, subject to criterion-based watermaze training, sacrificed 20 sec following a probe trial 7 days after learning the task, and b) a basal levels group, with no behavioral training. 12 WT and 11 APPtg mice were used in the behavioral work, which replicated the phenotype of our previous published work. Synaptosome forebrain samples from 16 mice (4 mice from each of the genotype/behavioral combinations) have been subjected to proteomics analysis. All procedures were performed blindly. Our results suggest higher levels of synaptic mitochondria in WT mice during memory retrieval compared to WT mice with no behavioral stimulus, a phenotype less evident in APPtg mice. Several other interesting processes seem to be also involved, such as proteasome activity. Western blot and mitochondrial respiration analyses are ongoing. Our data provide evidence supporting our hypothesis of stimulus-dependent mitochondrial transport to synapses as a mechanism underlying memory retrieval and its impairment in AD. The identification of additional pathways involved might also lead to new lines of research.

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Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

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Presentation Number: 014.09

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

Support: CPER CTRL 18 FEDER EqE - MC

Title: Dissimilar expression of Alzheimer’s disease risk factors in separate cell types of the adult human brain

Authors: D. M. COELHO[1], L. IOHAN[1], J.-C. LAMBERT[2], ***M. R. COSTA**[3,1];
[1]Brain Inst., Federal Univ. of Rio Grande do Norte, Natal, Brazil; [2]INSERM U1167, Inst. Pasteur de Lille, Lille, France; [3]INSERM U1167, Inst. Pasteur De Lille, Lille, France

Abstract: In the last decade, several genomic-wide association studies (GWAS) have identified genetic loci associated with the risk for late-onset Alzheimer's disease (LOAD). However, identification and further characterization of possible LOAD risk genes in those loci remains a challenge. As yet, from 49 LOAD risk loci identified, approximately 177 possible LOAD risk genes have been proposed, but the potential influences of these genes in AD pathology are still to be determined in animal or cellular models. In view of the high number of candidates, strategies to refine this list of risk genes are highly required before moving to experimental settings. We

hypothesized that analysis of gene expression patterns in different cell types of the adult human brain could contribute to pinpoint genes and networks associated with cellular processes known to be altered in AD. Towards this aim, we analyzed the expression of the mRNA of 177 LOAD and 3 early-onset Alzheimer's disease (EOAD) risk genes in single cells isolated from the adult brain. We found that only 147 of these genes were expressed by neural (neurons, astrocytes, oligodendrocytes and oligodendrocyte precursor cells) or microglial cells. More importantly, these cell types displayed different patterns of gene expression, with some AD risk factors expressed almost exclusively in specific cell types, such as PTK2B in neurons or APOE in astrocytes and microglia. Protein-protein interaction (PPI) analysis of genes expressed in individual cell types reveals protein cores associated with synaptic function, endocytosis, APP-processing and TAU pathology. These cores comprise different molecular players in glutamatergic, GABAergic, macroglial or microglial cells, suggesting that individual AD risk factors may have a more prominent impact in cellular functions of particular cell types. As a consequence, we propose that experimental models aiming at the investigation of AD risk factors should consider the cellular type in which the gene of interest is commonly expressed in the adult human brain. Our findings may contribute to better design experimental approaches to probe causal relations between risk genes identified in genomic studies and AD pathology.

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Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

Time: Saturday, October 19, 2019, 1:00 PM - 4:00 PM

Presentation Number: 014.10

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

Title: Deep proteomic profiling of CSF from subjects with Alzheimer’s disease using DIA mass spectrometry

Authors: *N. DUPUIS, R. BRUDERER, Y. FENG, D. HEINZMANN, L. REITER; Biognosys AG, Schlieren, Switzerland

Abstract: Background Cerebrospinal fluid (CSF) is established as a key matrix that enables interrogation of biological processes within the central nervous system. CSF biomarkers may support development of new therapies through patient stratification, determining prognosis, and response monitoring. However, the need for better biomarkers and biological understanding is evidenced by the lack of success of disease modifying drugs in late-stage clinical trials. Here, we seek to address this unmet need by applying an optimized workflow, based on data-independent acquisition mass spectrometry (DIA-MS), to deeply characterize the proteomes of CSF from subjects with Alzheimers’ Disease (AD). **Methods** CSF samples were obtained from subjects

with AD (n = 16) and age-matched controls (CO; n = 8). The samples were prepared using in solution digestion. A sample specific library was generated by pooling all samples and fractionating using high-pH reverse phase fractionation. Subsequently, the fractions were separated using 2h gradients and recorded by data-dependent acquisition on a Thermo Scientific Q Exactive HF-X mass spectrometer. Quantification was performed with DIA-MS on the same LC-MS setup using 2h gradients. DIA data analysis was conducted using Spectronaut™ (Biognosys) with peptide and protein false discovery rates set to 1%. **Results** A CSF library was generated covering 4,390 proteins. Across all samples 1,924 proteins were quantified in single shot acquisitions. The pool of quantified proteins comprises well characterized species associated with AD and other neurological disorders such as BACE1, APP, MAPT (Tau), SNCA, TREM2, YKL-40, and NEUG. Moreover, the depth and breadth of protein quantification covers numerous pathological mechanism (e.g. AB and Tau pathology, synaptic dysfunction, iron toxicity and inflammation). Differential expression analysis identified 41 proteins that are significantly dysregulated between AD and CO groups (Q-value < 0.05 and Log2 FC > 0.58). We observed several classes of proteins both up/down-regulated in AD samples including apolipoproteins (APO-A/B-100/L1), components of the complement system (C4BPA/B), regulators of synaptic functions (RGMA, LGI1 and CLSTN1) as well as markers for oxidative stress (SOD1 and PRDX2). Interestingly, in AD samples we found significantly higher level of CHIT1, an enzyme that responds to pathogen or bacterial infection and that is tightly linked to type I Gaucher disease. **Conclusions** Optimized DIA-MS enables simultaneous quantitative characterization of close to 2,000 proteins, covering >90% of developmental markers, from CSF with a workflow that is scalable to 100s of samples.

Disclosures: **N. Dupuis:** A. Employment/Salary (full or part-time):; Biognosys AG. **R. Bruderer:** A. Employment/Salary (full or part-time):; Biognosys AG. **Y. Feng:** A. Employment/Salary (full or part-time):; Biognosys AG. **D. Heinzmann:** A. Employment/Salary (full or part-time):; Biognosys AG. **L. Reiter:** A. Employment/Salary (full or part-time):; Biognosys AG.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

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Presentation Number: 014.11

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

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P50AG025688

Title: Integrative proteomics links CSF biomarkers to pathological brain networks in Alzheimer's disease

Authors: L. PING[1], L. HIGGINBOTHAM[1], E. DAMMER[1], D. M. DUONG[1], M. ZHOU[1], T. WINGO[1], E. C. B. JOHNSON[1], J. J. LAH[1], A. I. LEVEY[1], ***N. T. SEYFRIED**[2];
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Abstract: Alzheimer's disease (AD) features a complex web of pathological processes beyond amyloid accumulation and tau-medicated neuronal death. To meaningfully advance therapeutics, there is a need for novel AD biomarkers that comprehensively reflect these underlying disease mechanisms. We employed an integrative proteomic approach to identify protein alterations in AD CSF linked to a wide assortment of network-based pathophysiology in the diseased brain. Using tandem mass tags and mass spectrometry-based proteomics, we analyzed the CSF proteomes from 40 subjects (controls=20; AD=20) and brain proteomes from a separate cohort of 40 pathologically-confirmed cases (controls=10; Parkinson's disease (PD)=10; AD/PD=10; AD=10). Integrative statistical analyses were used to identify differentially abundant CSF proteins with strong links to functional co-expression networks in the diseased brain. Proteomic analysis of the CSF samples revealed 2,875 total proteins across cases, while the brain proteomic analysis identified ~9,000 proteins organized into 44 co-expression modules. Fifteen brain modules demonstrated statistically significant protein overlap in the CSF by Fisher's Exact Test analysis. The majority of these overlapping modules were also enriched with proteins with differential abundance in AD CSF. Collectively, these overlapping modules represented five functional brain processes: synaptic signaling, humoral immunity, myelination, glial response to injury, and energy metabolism. Proteins mapping to neuron-enriched synaptic and metabolic modules were overall decreased in the AD brain, but increased in AD CSF. Conversely, proteins mapping to glial-associated modules were increased in both brain and CSF. A panel of the most altered, easily detectable proteins among these brain-based CSF markers were successfully validated in a separate CSF cohort of AD cases. Our results provide a framework for identifying CSF protein biomarkers highly reflective of complex network-based AD pathophysiology that could potentially serve as therapeutic targets.

Disclosures: L. Ping: None. **L. Higginbotham:** None. **E. Dammer:** None. **D.M. Duong:** None. **M. Zhou:** None. **T. Wingo:** None. **E.C.B. Johnson:** None. **J.J. Lah:** None. **A.I. Levey:** None. **N.T. Seyfried:** None.

Nanosymposium

014. Proteome Dysfunction in Aging, Neurodegenerative Disorders, and Alzheimer's Disease

Location: Room S104

Time: Saturday, October 19, 2019, 1:00 PM - 4:00 PM

Presentation Number: 014.12

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

Support: NIH Grant P01 AG012411
NIH Grant R01 AG062254
VA Merit Grant I01 BX001655

Title: Glial fibrillary acidic protein: A biomarker and drug target for Alzheimer's and other neurodegenerative diseases

Authors: *R. J. SHMOOKLER REIS[1,2], A. GANNE[3,1], R. D. HENDRIX[1,4], M. BALASUBRAMANIAM[1], S. T. GRIFFIN[1,2], S. W. BARGER[1,2], S. AYYADEVARA[1,2]; [1]Geriatrics, Univ. of Arkansas for Med. Sci., Little Rock, AR; [2]Res., Central Arkansas Veterans Healthcare Syst., Little Rock, AR; [3]Bioinformatics, Univ. of Arkansas at Little Rock, Little Rock, AR; [4]Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Glial fibrillary acidic protein (GFAP) is a member of the intermediate filament family of structural proteins and is involved in cytoskeleton assembly and maintenance. Although expressed at low levels in many cell types, GFAP was named for its highly induced synthesis in activated glial cells. It appears to be neuroprotective, because GFAP knockout mice are hypersensitive to traumatic brain injury. GFAP in cerebrospinal fluid is a biomarker of Alzheimer's disease (AD), dementia with Lewy bodies, and frontotemporal dementia. We here present novel evidence that GFAP is markedly overexpressed and differentially phosphorylated in AD, especially in the hippocampus of AD persons homozygous for the ε4 allele of *APOE*. Moreover, GFAP is particularly enriched in detergent-insoluble aggregates in AD brain, relative to age-matched controls. *In silico* analysis indicates four kinases that could be responsible for the observed site-specific phosphorylations of GFAP in AD brain, all of which were shown to be upregulated in AD. We tested the roles of these kinases in SH-SY5Y cells that accumulate amyloid β-peptide due to stable transfection with the Swedish mutant of amyloid precursor protein (APP_{Sw}). Knockdown of the prospective GFAP kinases reduced accumulation of amyloid, as indicated by thioflavin T staining of these cells. Moreover, knockdown of the orthologous kinases in *C. elegans* reduced aggregation and its associated paralysis in multiple models of Alzheimer's-like amyloidosis as well as a model of Huntington's disease. These data indicate that phospho-GFAP plays a crucial role in progression of protein aggregation and neurotoxicity during neurodegeneration; thus GFAP and its specific phosphorylated species could serve as both valuable biomarkers and novel drug targets for Alzheimer's disease and related disorders.

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Nanosymposium

015. Neurodegeneration and Injury I

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Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.01

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

Support: NIA/NIH R01AG042890
NIH/NIA R01AG060718

Title: Functional integrity of synapses is associated with absence of synaptic tau oligomers in the cns of cognitively-intact individuals with high Alzheimer's neuropathology

Authors: B. TUMURBAATAR[1], A. SINGH[1], B. KRISHNAN[1], C. NATARAJAN[1], A. LIMON[1], P. SCADUTO[1], R. WOLTJER[2], R. KAYED[1], ***G. TAGLIALATELA**[1];
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Abstract: Some individuals, here referred to as Non-demented with Alzheimer's disease Neuropathology (NDAN), remain cognitive intact despite the presence of Alzheimer's Disease (AD) neuropathology (amyloid plaques and tau tangles) normally associated with fully symptomatic AD. Understanding the mechanisms involved in such resilience could reveal new targets for the development of a novel therapeutic concepts centered on inducing resistance in anyone affected by AD. With this goal in mind, here we used autopsy brain specimens from AD patients and NDAN subjects to determine the synaptic presence of toxic tau oligomers (a key driver of AD cognitive deficits) and evidence of synapse functional integrity. Total and oligomeric tau in hippocampus and frontal cortex was evaluated by IHC in brain sections and by ELISA/immunoprecipitation(IP)/western blotting/mass spectrometry (MS) in isolated synaptosomes. Synaptosomes were also used to assess chemical long term potentiation (cLTP) and electrophysiology of reactivated human receptor after micro transplantation of synaptic membranes (MSM) in Xenopus oocytes. We found decreased tau oligomers in the brains of NDAN versus AD patients and determined that increasing levels of tau oligomers correlate with cognitive deterioration. Furthermore, while abundant tau oligomers were observed in synaptosomes from AD patients, there were no tau oligomers in synaptosomes from non-demented NDAN subjects. On the other hand, using IP and MS in these latter we detected a unique, non-amyloid hybrid protein aggregate comprising tau and Amyloid beta that appears to sequester tau from forming higher molecular weight toxic oligomers within synapses. Lastly, absence of tau oligomers in NDAN synapses was associated with intact cLTP expression and preserved Excitatory/Inhibitory (E/I) ratio as determined by MSM. These results contribute one possible mechanism for the preserved cognition found in NDAN individuals and link low levels of tau oligomers and their absence at synapses to maintenance of synaptic function and retention of cognitive integrity in humans despite the conspicuous presence of NFTs and amyloid plaques, giving further credence to tau oligomers as important therapeutic targets in AD.

Disclosures: **B. Tumurbaatar:** None. **A. Singh:** None. **B. Krishnan:** None. **C. Natarajan:** None. **A. Limon:** None. **P. Scaduto:** None. **R. Woltjer:** None. **R. Kayed:** None. **G. Taglialatela:** None.

Nanosymposium

015. Neurodegeneration and Injury I

Location: Room S401

Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

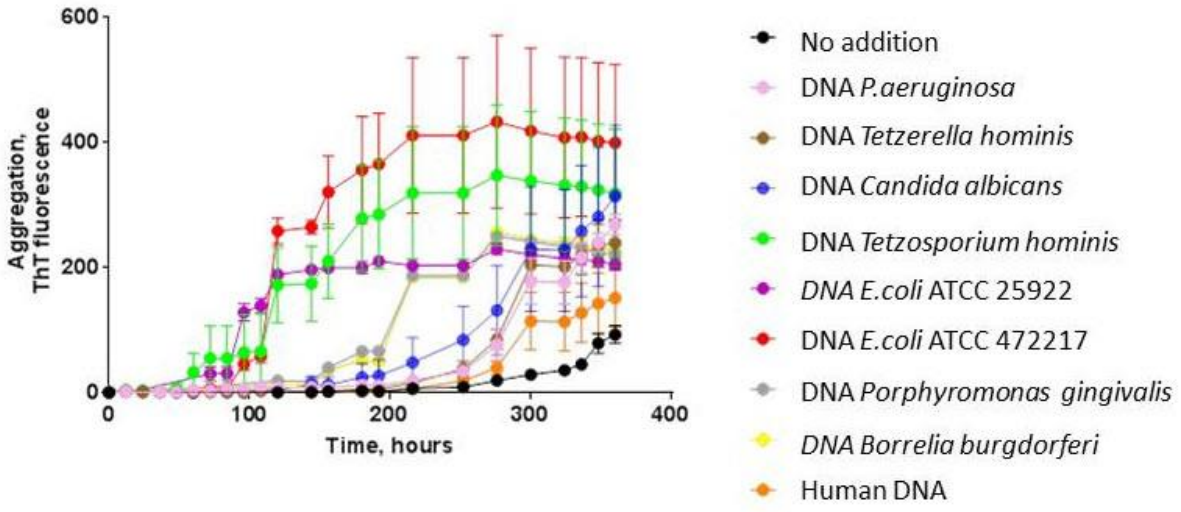
Presentation Number: 015.02

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

Title: Bacterial DNA promote tau aggregation

Authors: *G. TETZ[1], M. PINHO[2], S. PRITZKOW[3], N. MENDEZ[2], C. A. SOTO[4], V. TETZ[1]; [1]Human Microbiology Inst., New York, NY; [2]Mitchell Ctr. for Alzheimer's Dis. and Related Brain Disorders, Huston, TX; [3]Neurol., Uthealth Sci. Ctr. at Houston, Houston, TX; [4]The Univ. of Texas Hlth. Sci. Center- Houston Med. Sch., Houston, TX

Abstract: Background Different bacteria (including facultative intracellular parasites) and fungi have been detected in the cerebrospinal fluid and postmortem brains of individuals with Alzheimer's disease. We hypothesize that DNA from these microorganisms can act as an efficient promoter for protein misfolding in AD pathogenesis. In this study, we evaluated the effect of DNA extracted from diverse prokaryotic and eukaryotic cells in tau misfolding and aggregation. Our results show that DNA from various, unrelated gram-positive and gram-negative bacteria may play a previously overlooked role in the propagation of tau protein misfolding and AD pathogenesis
Methods Full-length human Tau (1 mg/ml) subjected to cyclic agitation was incubated with or without different concentrations of DNA from different Gr+/- bacteria, fungi and human cells to evaluate Tau aggregation. **Results** The results showed that DNA from various (but not all) bacterial species significantly promoted tau aggregation. Conversely, addition of eukaryotic DNA, such as from yeast or human cells, had a much lower effect in promoting tau aggregation. (Fig 1. Evaluation of bacterial eDNA on Tau aggregation). Comparisons of the lag phases indicate that the largest promoting effect (shorter lag phase) was obtained in the presence of Escherichia coli. **Conclusions** Here we report the first evidence for the capacity of extracellular DNA from certain bacterial species to substantially promote tau misfolding and aggregation.



Disclosures: **G. Tetz:** None. **M. Pinho:** None. **S. Pritzkow:** None. **N. Mendez:** None. **C.A. Soto:** None. **V. Tetz:** None.

Nanosymposium

015. Neurodegeneration and Injury I

Location: Room S401

Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.03

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

Support: NIH Grant T32GM118292-02
NIA Grant RF1AG057754

Title: Association of herpesviruses with Alzheimer’s disease and vascular contributions to cognitive impairment and dementia in human brain

Authors: *C. E. SEAKS, IV[1], C. M. KLOSKE[2], A. WOOLUMS[4], S. ANDERSON[1], E. PATEL[1], E. M. WEEKMAN[2], T. L. SUDDUTH[5], E. L. ABNER[1], P. T. NELSON[1], R. DUTCH[3], D. M. WILCOCK[1];
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Abstract: Alzheimer’s disease (AD) is the leading cause of dementia worldwide followed by vascular contributions to cognitive impairment and dementia (VCID). The etiologies and precise pathogenesis of both diseases have not been fully elucidated, however, the associations between

different bacterial and viral infections with AD are being discovered at increasing frequency. Recent animal and human studies have connected multiple herpesviruses to the development and pathogenesis of AD. There is also a strong connection between AD and VCID, with nearly 60% of AD cases presenting with a VCID co-morbidity. Despite this common comorbidity, the prevalence of herpesvirus infections in VCID patients has not been extensively studied. The goal of this study was to determine the prevalence of four common herpesviruses in a cohort of AD and VCID patients, and to identify risk factors and interacting genes of interest. We hypothesized that cases with more severe VCID pathology would have higher viral loads as compared to less severe or healthy cases. Using droplet-based PCR, we quantified the prevalence of four common herpesviruses (herpes simplex virus 1, herpes simplex virus 2, cytomegalovirus, and human herpes virus 6) in a subset of brain autopsy tissue obtained from the Sanders-Brown Center on Aging. We extracted RNA from sub-medial temporal gyrus (SMTG), a region adjacent to the hippocampus where AD and VCID pathology are expected, as well as the cerebellum which serves as an internal control due to the typical lack of AD and VCID pathology (n=19 primarily AD diagnosed cases, n=5 non-AD controls, both SMTG and cerebellum from each case used). Genomic DNA was used to determine the presence of latent virus and cDNA to determine actively replicating virus. The RNA from these regions was used to perform a 757 probe NanoString neuroinflammatory panel (nCounter ™ Human Neuroinflammation Panel) looking at a wide range of genes of interest, ranging from neuroinflammatory markers to cell specific functional genes. Our results provide valuable data about the association between herpesviruses and not only AD, but also VCID. Additionally, our studies characterizing the genetic background of these patients have identified potential risk factors for chronic infection of the central nervous system by herpesviruses.

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Nanosymposium

015. Neurodegeneration and Injury I

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Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.04

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

Support: NIH Grant T32 AG057461

Title: VCID brains show significant gene expression alterations in myelin-associated and microglial function genes within the frontal cortex relative to low pathology cognitively normal brains

Authors: *K. E. SALMERON[1], T. L. SUDDUTH[7], D. HAWTHORNE[2], B. R. PRICE[3], E. M. WEEKMAN[3], P. T. NELSON[4], S. ANDERSON[5], E. PATEL[5], G. JICHA[6], D. M. WILCOCK[5]; [1]Sanders Brown Ctr. on Aging, Univ. of Kentucky, Lexington, KY; [2]Univ. of Kentucky, Belleville, IL; [3]Physiol., [4]Neuropathology, [6]Neurol., [5]Univ. of Kentucky, Lexington, KY; [7]Sanders-Brown, Univ. of Kentucky Chandler Med. Ctr., Lexington, KY

Abstract: Vascular contributions to cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer's disease (AD). Additionally, VCID is frequently co-morbid with AD, which complicates the diagnosis and treatment of both diseases. Unfortunately, VCID remains understudied compared to AD and little is known about its pathogenesis and progression. One of the more disruptive and unique pathologies associated with VCID's progression is white matter degeneration. Additionally, one of the earliest hallmarks of many neuroinflammatory diseases is microglial activation. In this proposal we tested the hypothesis that neuroinflammatory gene expression patterns within the frontal cortex of VCID patients significantly differ from those of non-VCID patients. To test this hypothesis, we first examined the brains of autopsy cases of VCID and age matched, cognitively normal controls (lacking any neurodegenerative pathology). We used the Human Neuroinflammation NanoString panel to assess the inflammatory profile in the frontal cortices and cerebellum of post-mortem VCID (n=8) and non-VCID (n=18) patients. Using the nSolver software, we analyzed 770 genes broadly associated with neuroinflammatory processes and found that 112 genes significantly differed in the VCID group vs the non-VCID group. Following a Benjamini-Hochberg procedure of False Discovery Rate (FDR) Analysis, a fold change exclusion (fold changes within +/- 1.5 were excluded), and a gene count exclusion (gene counts of less than 100 were excluded), we found 15 genes of interest. We then tested those genes of interest: (TNFRSF25, HSPB1, CD8A, P2RY12, TMEM144, TNFSF4, BLNK, MAL, NINJ2, MAG, OPALIN, PLLP, GJB1, IGSF6, and CX3CR1) on qPCR in order to verify consistent trends from our NanoString analysis. While most trends were conserved, those associated with apoptosis as well oligodendrocyte and microglia function were the most affected. Taken together, this study shows clear genetic patterns associated with white matter integrity and microglia function and indicates a clear need for the continued investigation of VCID's neuroinflammatory mechanisms.

Disclosures: K.E. Salmeron: None. **T.L. Sudduth:** None. **D. Hawthorne:** None. **B.R. Price:** None. **E.M. Weekman:** None. **P.T. Nelson:** None. **S. Anderson:** None. **E. Patel:** None. **G. Jicha:** None. **D.M. Wilcock:** None.

Nanosymposium

015. Neurodegeneration and Injury I

Location: Room S401

Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.05

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

Support: NS085770

Title: Status of prefrontal cortex synaptic proteins in frontotemporal lobar degeneration with TDP-43 pathology

Authors: *I. A. AYALA, Y. PAN, A. BAHRAMI, S. LAMERAND, R. SHAHIDEHPOUR, T. GEFEN, E. BIGIO, M. MESULAM, *C. GEULA;
Northwestern Univ. Med. Sch., Chicago, IL

Abstract: In dementia due to Alzheimer's disease (AD), loss of cortical synaptic proteins and decreased synaptic number are among the earliest neuronal alterations detected in the course of the disease, and display the strongest relationship with severity of impairment. Aberrant synaptic pruning by microglia has been implicated in the early loss of synapses in AD. However, the status of synaptic alterations and abearant pruning by microglia in dementia due to frontotemporal lobar degeneration (FTLD), and particularly the pathological subtype caused by accumulation and aggregation of the tar DNA binding protein-43 (TDP-43, FTLD-TDP) remain relatively unexplored. The current study investigated levels of the pre-synaptic protein synaptophysin (STP), the post-synaptic protein PSD-95, and the dendritic spine protein spinophilin (SNH), in fresh-frozen homogenates of prefrontal cortex (middle frontal gyrus; Broadmann area 9) in brains from cognitively normal cases and in brains of individuals with FTLD-TDP. Western blot analysis was performed for detection of proteins using specific antibodies and optical density of bands was expressed as percentage of the housekeeping protein GAPDH. Reductions were detected in STP, SPH and PSD-95 in FTLD-TDP cases compared to controls (56%, 35% and 14%, respectively). Reductions in STP were statistically significant ($p<0.03$). To determine whether there was evidence of aberrant synaptic pruning by microglia in FTLD-TDP, we identified STP, SPH and PSD-95 within microglia in cases with FTLD-TDP and in a conditionally transgenic mouse model overexpressing wild-type human TDP-43 in forebrain neurons. Double fluorescence immunohistochemistry revealed accumulation of all three synaptic proteins within microglia in the prefrontal cortex of both FTLD and TDP-43 transgenic mice. Together, these preliminary findings suggest significant loss of synaptic proteins and reduced levels of dendritic spines in FTLD-TDP. The observation that microglia display significant phagocytosis of synaptic proteins in FTLD-TDP raises the possibility of aberrant synaptic pruning in this disorder.

Disclosures: I.A. Ayala: A. Employment/Salary (full or part-time):; Northwestern University. **Y. Pan:** None. **A. Bahrami:** None. **S. Lamerand:** None. **R. Shahidehpour:** None. **T. Gefen:** None. **E. Bigio:** None. **M. Mesulam:** None. **C. Geula:** None.

Nanosymposium

015. Neurodegeneration and Injury I

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Presentation Number: 015.06

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

Support: Academy of Finland Grant 315459
Yrjö Jahnsson Foundation Grant 20187070
Doctoral Program in Molecular Medicine, University of Eastern Finland

Title: Regulation of C9orf72 proteins in neuronal cells and their function in autophagy and ubiquitin proteasome system

Authors: *S. LESKELÄ[1], N. HUBER[1], H. ROSTALSKI[1], J. LIST[1], M. CARTRÓ FONT[1], A. M. REMES[3,4], M. TAKALO[2], M. HILTUNEN[2], A. HAAPASALO[1];
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Abstract: Hexanucleotide repeat expansion (HRE) in the *C9orf72* gene is a major genetic factor underlying frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Both loss-of-function and gain-of-toxic-function mechanisms, including haploinsufficiency and formation of toxic intranuclear RNA foci and dipeptide repeat proteins, are suggested to contribute to the pathogenesis of *C9orf72*-HRE-linked FTD and ALS. In addition to these, dysfunction of protein degradation pathways, including ubiquitin-proteasome system (UPS) and autophagy has been implicated. The normal physiological functions of *C9orf72*, which produces two different protein isoforms A and B in humans, are only beginning to unravel. C9orf72 isoform A is suggested to regulate autophagy, but current data on whether C9orf72 activates or inhibits autophagy have been partially controversial. We have utilized overexpression of C9orf72 isoforms A and B or shRNA-mediated knockdown of endogenous *C9orf72* in N2a mouse neuroblastoma cells and cultured mouse primary cortical neurons to elucidate the normal functions of C9orf72 proteins and model the loss-of-function mechanism taking place in patients carrying *C9orf72* HRE. To modulate protein degradation pathways, we used lactacystin to inhibit the UPS, serum starvation or rapamycin treatment to induce autophagy, and bafilomycin A1 (BafA1) to block autophagosomal degradation. Proteasomal function was assessed by proteasomal activity kit. No changes in autophagy nor proteasomal activity in N2a cells overexpressing either of the C9orf72 isoforms were observed. In contrast, knockdown of *C9orf72* in N2a cells led to a decrease in LC3BI to LC3BII conversion and p62 degradation, suggesting compromised autophagy. Immunofluorescent studies revealed fewer LC3-containing autophagosomes in *C9orf72* knockdown cells upon serum starvation-induced autophagy when compared to control cells. In addition, proteasomal activity was slightly decreased in N2a cells upon *C9orf72* knockdown. After proteasomal inhibition, the levels of both C9orf72 isoforms significantly increased in N2a cells and primary neurons, suggesting that C9orf72 protein levels are regulated by proteasomal degradation. Induction of autophagy led to decreased levels of both C9orf72 isoforms in N2a cells. These were restored by lactacystin treatment, but not BafA1 treatment, implying that C9orf72 proteins may be targeted to proteasomal degradation upon induction of autophagy. Our

studies provide further insights into the regulatory role of C9orf72 in autophagy and suggest that C9orf72 levels are controlled via UPS-mediated degradation.

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Nanosymposium

015. Neurodegeneration and Injury I

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Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.07

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

Support: NINDS NS085770
NIDCD DC008552
NIA AG013854

Title: Neuronal number and size display concordance with disease phenotype in primary progressive aphasia with TDP-43 pathology

Authors: G. KIM[1], I. A. AYALA[2], S. LAMERAND[3], R. SHAHIDEHPOUR[4], T. GEFEN[5], *S. WEINTRAUB[6], E. BIGIO[2], M.-M. MESULAM[7], C. GEULA[8];
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Abstract: Primary progressive aphasia (PPA) is a neurodegenerative disorder in which loss of language function is the most salient clinical feature. PPA is characterized by significant atrophy in the perisylvian language network in the language dominant hemisphere (LDH). A proportion of PPA brains present with TDP-43 containing inclusions in the brain at autopsy (PPA-TDP). We previously showed that the density of TDP-43 inclusions and activated microglia in PPA-TDP display concordance with disease phenotype; they are more prominent in language cortical regions and show significant asymmetry favoring the LDH. TDP-43 inclusions also predominate in areas of greatest atrophy. The purpose of this experiment was to determine whether neuronal number and size display similar concordance with disease phenotype. The density of Nissl-stained cortical pyramidal neurons were determined in the language cortical areas including inferior frontal gyrus (IFG), inferior parietal lobule (IPL) and superior temporal gyrus (STG), and the memory-related entorhinal cortex (EC), in a cohort of PPA-TDP brains using unbiased

stereological counting techniques. Perikaryal area of neurons in layers III and V of these regions was also determined in both LDH and the non-language dominant hemisphere (NLDH), using the Image J software. Across regions, the number of neurons was slightly but consistently lower in the LDH compared to same regions in NLDH. Size of layer V neurons showed more consistent asymmetry and was smaller in the LDH in the language-related IPL and STG, but not in the memory-related EC. The hemispheric asymmetry of layer V pyramidal neuronal size reached statistical significance in STG ($p<0.02$). A case with language function localized to the right hemisphere by functional MRI showed consistently smaller neuronal size in the right hemisphere across all regions ($p<0.0001$). These preliminary findings suggest that neuronal size and to a lesser extent neuronal number show alterations in PPA-TDP that are consistent with regional specificity and asymmetry of language function.

Disclosures: **G. Kim:** None. **I.A. Ayala:** None. **S. Lamerand:** None. **R. Shahidehpour:** None. **T. Gefen:** None. **S. Weintraub:** None. **E. Bigio:** None. **M. Mesulam:** None. **C. Geula:** None.

Nanosymposium

015. Neurodegeneration and Injury I

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Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.08

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

Support: Research Funding for Longevity Sciences from National Center for Geriatrics and Gerontology Japan (19-7)
Japan Society for the Promotion of Science KAKENHI JP (JP16K08637)
Takeda Science Foundation
DAIKO Foundation
JSPS KAKENHI (Grant-in-Aid for Early-Career Scientists), 19K17022

Title: Sur deficiency increases vulnerability to age-related neurodegeneration in *Drosophila*

Authors: *X. QUAN[1], M. SEKIYA[2], Y. SAKAKIBARA[2], K. M. IIJIMA[2];
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Abstract: Hippocampal sclerosis of aging (HS-aging) is characterized by neuronal cell loss and gliosis in the hippocampus frequently accompanied by TAR-DNA binding protein-43 (TDP-43) pathology. Clinically, HS-aging mimics Alzheimer’s disease (AD) with memory loss and decreased cognition. Interestingly, besides amyloid plaques and neurofibrillary tangles, TDP-43 pathology was also observed in AD brains, suggesting a potential mechanism linking HS-aging and AD. Sulfonylurea receptor 2 (*ABCC9*/SUR2) is the regulatory subunit of ATP-sensitive potassium channels and has been reported as one of the risk factors for HS-aging. However, the

effects of *ABCC9*/SUR2 dysfunctions on age-related neurodegeneration and formation of TDP-43 pathology are unknown. Using *Drosophila* as an *in vivo* model, here we investigated neuroprotective roles of *Sur*, a fly ortholog of *ABCC9*/SUR2, during aging. While *Sur* deficiency by itself did not cause prominent neurodegeneration, it significantly worsened behavioral deficits and neurodegeneration in a *Drosophila* model of Aβ42 toxicity, suggesting neuroprotective roles of *Sur* in flies. Intriguingly, *Sur* deficiency significantly increased mRNA expression levels of *dTARDBP*/dTDP-43, a fly ortholog of TDP-43, in Aβ42 fly brains. Moreover, neuronal knockdown of *dTARDBP*/dTDP-43 significantly worsened behavioral deficits in Aβ42 flies with *Sur* deficiency, suggesting that induction of *dTARDBP*/dTDP-43 may be a neuroprotective response against *Sur* deficiency. In summary, our results suggest potential links among *Sur* deficiency, vulnerability to age-related neurodegeneration, and initiation of TDP-43 pathology.

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Nanosymposium

015. Neurodegeneration and Injury I

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Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.09

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

Support: NIH Grant RO1NS107396

Title: Mitochondrial impairment in FUS proteinopathy

Authors: *M. TAKACS, W. A. MCGEE, X. CHEN, K. FUSHIMI, J. WU;
Neurol., Ctr. for Genet. Medicine, Lurie Cancer Center, Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: FUS (Fused in sarcoma), an RNA/DNA binding protein, has been linked to many neurodegenerative disorders including amyotrophic lateral sclerosis (ALS) and frontotemporal lobe dementia (FTD). FUS regulates a range of functions in cells, including DNA damage repair, transcription, post-transcriptional RNA processing, stress granule formation and mitochondria dysfunction. Our recent work shows that mutations in or upregulation of the FUS gene leads mitochondrial damage and triggers the mitochondrial unfolded protein response (UPR^{mito}). However, it is unclear whether such mitochondrial impairment is a driving event or one of the many consequences of FUS proteinopathy. We aim to fill this critical knowledge gap by characterizing the gene networks that are regulated by FUS and determining their role in FUS proteinopathy using cellular and animal models. Detailed experimental data and the implications will be discussed during the meeting.

Disclosures: **M. Takacs:** None. **W.A. McGee:** None. **X. Chen:** None. **K. Fushimi:** None. **J. Wu:** None.

Nanosymposium

015. Neurodegeneration and Injury I

Location: Room S401

Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.10

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

Support: NIH Grant RO1NS107396

Title: Mitochondrial unfolded protein response and mitochondrion-mediated protein degradation

Authors: ***F. H. ZHOU**, M. TAKACS, W. MCGEE, X. CHEN, K. FUSHIMI, J. Y. WU; Neurol., Northwestern Univ., Chicago, IL

Abstract: Dys-regulation of and mutations in the human TDP-43 gene have been associated with TDP-43 proteinopathy, a group of neurodegenerative diseases including fronto-tempro lobar degeneration (FTLD-TDP) and motor neuron disease such as ALS. TDP-43 positive pathology has been found in ~50% brain samples from patients affected by Alzheimer's disease and brain samples of traumatic brain injury. Although mitochondrial localization of TDP-43 has been reported, the effects of TDP-43 in mitochondrial damage and neuronal loss remain controversial (see Wang et al, 2016; Kawamata et al, 2017). We have carried out a systematic study combining analyses of patient brain samples with cellular and animal models for TDP-43 proteinopathy. Electron microscopy (EM) analyses of patient samples revealed severe mitochondrial impairment, including abnormal cristae and loss of cristae; these ultrastructural changes were consistently observed in both cellular and animal models of TDP-43 proteinopathy. In all these models, increased expression of TDP-43 induced mitochondrial functional impairment, including decreased mitochondrial membrane potential, elevated production of reactive oxygen species (ROS) and reduced mitochondrial ATP synthesis. Importantly, expression of wild type or ALS-mutant TDP-43 activated the mitochondrial unfolded protein response (UPR^{mt}) in both cellular and animal models. Down-regulating mitochondrial LonP1 protease increased mitochondrial TDP-43 levels and exacerbated TDP-43 induced mitochondrial damage as well as neurodegeneration. Together, our data demonstrate that TDP-43 induced mitochondrial impairment is a critical aspect in TDP-43 proteinopathy. Our work has uncovered a previously unknown role of LonP1 in regulating mitochondrial TDP-43 levels and also suggests targeting mitochondrial damage as a potential therapeutic approach to these devastating diseases. More details will be presented and discussed.

Disclosures: **F.H. Zhou:** None. **M. Takacs:** None. **W. Mcgee:** None. **X. Chen:** None. **K. Fushimi:** None. **J.Y. Wu:** None.

Nanosymposium

015. Neurodegeneration and Injury I

Location: Room S401

Time: Saturday, October 19, 2019, 1:00 PM - 3:45 PM

Presentation Number: 015.11

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

Support: National Multiple Sclerosis Society
Center for Multiple Sclerosis and Autoimmune Neurology
Mayo Clinic Biorepository

Title: Altered signatures in skin fibroblasts derived from patients with multiple sclerosis

Authors: *J. M. WILKINS, O. GAKH, P. KABIRAJ, C. MCCARTHY, O. TOBIN, C. HOWE, C. LUCCHINETTI;
Mayo Clin., Rochester, MN

Abstract: Background: Multiple sclerosis (MS) is the most common form of neurodegeneration in young adults with no cure. The disease is characterized by chronic inflammation, demyelination, and the formation of lesions in the central nervous system. While the exact mechanisms that drive MS are unknown, it is likely to be driven by a combination of environmental stressors and multiple genetic variants. Studies using human tissue and mouse models suggest that multiple neural cell lines including oligodendrocytes, astrocytes, and neurons have perturbed bioenergetic profiles that contribute towards the pathogenesis and progression of MS. Therefore, we hypothesized that inherent defects associated with MS would induce bioenergetic stress in patient-derived skin fibroblasts. **Methods:** We utilized multiple assays to detect signatures of bioenergetic stress in patient-derived skin fibroblasts. Age- and sex-matched skin fibroblasts from MS and control patients were assayed for (1) altered metabolic function by measuring lactate production and use of metabolomics, (2) endoplasmic reticulum (ER) stress markers using qPCR, (3) cellular senescence by qPCR, and (4) cytotoxic effects of oxidative stress assessed by the MTT assay. **Results:** Metabolic alterations were detected in MS skin fibroblasts when compared to controls. Increased lactate production and altered levels of the tricarboxylic acid (TCA) cycle intermediates were detected. Markers of ER stress were significantly increased in MS skin fibroblasts compared to controls. When exposed to gamma irradiation, we found increased expression of cellular senescence markers. Lastly, inducing oxidative stress caused greater cytotoxic effects in MS skin fibroblasts compared to controls. **Conclusion:** This work suggests that inherent bioenergetic abnormalities associated with MS extends to patient-derived skin fibroblasts. Therefore, skin fibroblasts may serve as a clinically relevant tool for the diagnosis, prognosis, and testing of therapeutic efficacy enhancing individualized medicine. Furthermore, as skin fibroblasts can be differentiated into biologically relevant neural cell lines implicated in the pathogenesis of MS (e.g. oligodendrocytes, astrocytes,

neurons, etc.), this work highlights the utility of using primary cells to serve as models to study pathophysiological mechanisms of MS.

Disclosures: **J.M. Wilkins:** None. **O. Gakh:** None. **P. Kabiraj:** None. **C. McCarthy:** None. **O. Tobin:** None. **C. Howe:** None. **C. Lucchinetti:** None.

Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.01

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH RO1 NS096352
NIH F31 NINDS 106777-01

Title: Striatal projection neurons require Huntingtin for synaptic connectivity and longevity

Authors: *C. BURRUS[1], S. U. MCKINSTRY[1], N. KIM[1], F. Y. FANG[2], A. SANTOKI[1], H. H. YIN[3], C. EROGLU[4];
[2]Trinity Col. of Arts and Sci., [3]Dept. of Psychology and Neurosci., [1]Duke Univ., Durham, NC; [4]Cell Biol Dept, Duke Univ, DUMC, Durham, NC

Abstract: Huntington’s Disease (HD) is a fatal, inherited disease caused by an autosomal dominant polyglutamine expansion mutation near the N-terminus of the Huntingtin (Htt) protein. Patients with HD suffer from progressive motor, cognitive, and psychiatric impairments, along with significant degeneration of the striatal projection neurons (SPNs) of the striatum. The dominant nature of the Htt mutation has led to the widely-accepted hypothesis that HD is caused by a toxic gain-of-function of mutant Htt protein. Recent findings suggest that loss of Htt function due to dominant-negative effects of the mutant protein also play important roles in HD. However, the role of Htt in the health and function of the SPNs is not yet known, leaving critical aspects of HD pathology unexplored. To investigate this question, here we conditionally deleted Htt from specific subpopulations of striatal projection neurons (SPNs) using the Cre-Lox system. We determined that loss of Htt in SPNs leads to aberrant synaptic connectivity and function within the basal ganglia, along with dysregulated motor function. We also discovered that SPNs require Htt for longevity, as SPNs lacking Htt (Htt cKO) degenerate in an aging-dependent manner. Many Htt cKO SPNs display increased nuclear invagination, a feature of non-apoptotic cell death. We also found evidence for abnormal gene expression in Htt cKO SPNs. Intriguingly, we found a reduction in the expression of the dopamine signaling downstream integrator, DARPP-32, whose expression is also known to be sharply reduced in HD mouse models and patient brain tissue. Taken together, our findings show that loss of Htt function in SPNs impairs

basal ganglia synaptic connectivity and neuronal longevity, suggesting that Htt loss-of-function could play a critical role in HD pathogenesis.

Disclosures: C. Burrus: None. **S.U. McKinstry:** None. **N. Kim:** None. **F.Y. Fang:** None. **A. Santoki:** None. **H.H. Yin:** None. **C. Eroglu:** None.

Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.02

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Small molecule perturbation of Huntingtin conformations to disrupt toxic aggregate formation in cells

Authors: *C. H. LO[1], N. K. PANDEY[2], C. K. W. LIM[1], Z. DING[1], M. TAO[2], D. D. THOMAS[1], R. LANGEN[2], J. N. SACHS[1];
[1]Univ. of Minnesota, Minneapolis, MN; [2]USC, Los Angeles, CA

Abstract: Huntington’s disease (HD) is the most common inherited neurodegenerative disorder and one of the nine polyglutamine (polyQ) diseases characterized by the pathological aggregation of the misfolded huntingtin protein with abnormally long polyQ expansion due to genetic mutation. Recent studies suggest that HD is a conformational disease and perturbing huntingtin protein conformations may be more effective in targeting the toxic aggregates. To exploit this new therapeutic window, we engineered three FRET based biosensors that monitor the conformations of huntingtin (HTT) exon 1 with different polyQ lengths (Q16, Q39 and Q72) in living cells. These FRET biosensors, together with a high-precision fluorescence lifetime detection platform, enable high-throughput screening of small molecules that target HTT conformations. We found six small molecules that perturbed HTT conformations and reduced HTT-induced neuronal cell cytotoxicity with low micromolar to submicromolar potency. In addition, these compounds altered FRET in HTT biosensors of shorter polyQ lengths, suggesting that they were acting through perturbing the protein conformations rather than directly binding to the beta-sheet aggregates. Using SPR and an advanced EPR technique, we confirmed that the compounds directly bind to both monomeric HTT proteins as well as HTT fibrils and disrupt the huntingtin aggregation. This strategy in targeting the HTT conformations can be applicable to other proteins involved in polyQ diseases.

Disclosures: C.H. Lo: None. **N.K. Pandey:** None. **C.K.W. Lim:** None. **Z. Ding:** None. **M. Tao:** None. **D.D. Thomas:** None. **R. Langen:** None. **J.N. Sachs:** None.

Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.03

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: HDSA Grant

Title: Therapy-mediated reduction of cerebrospinal fluid mutant Huntingtin protein: What does it mean?

Authors: N. S. CARON[1], E. D. SMITH[2], C. YANICK[2], S. E. SMITH[3], J.-J. SONG[4], I. SEONG[5], B. R. LEAVITT[6], M. R. HAYDEN[7], ***A. L. SOUTHWELL**[2];
[1]Med. Genet., Ctr. for Mol. Med. and Therapeut., Vancouver, BC, Canada; [2]Burnett Sch. of Biomed. Sci., Univ. of Central Florida, Orlando, FL; [3]Ctr. for Integrative Brain Res., Seattle Childrens Res. Inst., Seattle, WA; [4]Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [5]Molec Neurogenetics, Massachusetts Gen Hosp, Boston, MA; [6]Dept. of Med. Genet., Ctr. For Mol. Med. & Therapeut., Vancouver, BC, Canada; [7]Univ. of Brithish Columbia, Vancouver, BC, Canada

Abstract: Huntington disease (HD) is a fatal neurodegenerative disorder caused by expansion of a CAG repeat in the huntingtin (*HTT*) gene. While mutation carriers can be identified decades in advance, there are currently no therapies that can delay onset or slow progression of the disease. HD pathogenesis is complex, thus, targeting the cause of the disease, mutant (mt)HTT, has appeal. In fact, a variety of HTT lowering strategies have shown preclinical promise, and several clinical trials are now underway. Pharmacodynamic biomarkers are needed for these trials. We previously developed an ultrasensitive immunoprecipitation and flow cytometry (IP-FCM) mtHTT detection assay and determined that cerebrospinal fluid (CSF) mtHTT responds to changes in brain mtHTT. Furthermore, the first HTT lowering safety trial has demonstrated dose-dependent reduction of CSF mtHTT. We are now using IP-FCM to query what this exciting new data tells us about therapeutic activity in the brain. The source of CSF mtHTT is unknown. Some therapeutics may be most active in regions in contact with the CSF. If these regions are the major sources of CSF mtHTT protein, then CSF-based predictions of HTT lowering in deeper structures may not be straightforward. Conversely, if regional contributions to CSF mtHTT are similar, then changes in CSF mtHTT level could be used to more accurately infer changes in basal ganglia mtHTT. Thus, we are interrogating the source(s) of CSF mtHTT protein using Hu97/18 mice (floxed mtHTT exon 1) crossed to brain region and cell type-specific cre mice as well as ectopic delivery of mtHTT to restricted brain regions. Additionally, we do not know how mtHTT enters CSF. CSF mtHTT is not detected in all premanifest HD mutation carriers and

acute brain injury causes a transient increase in CSF mtHTT, suggesting that mtHTT is released from dying neurons. Thus, any neuroprotective therapy would be expected to reduce it, and HTT lowering treatment-induced changes may represent neuroprotection. However, we have observed mtHTT in the CSF of mice lacking neurodegeneration, and a neuronal secretion pathway for mtHTT was recently identified, suggesting that there may be both passive and active clearance mechanisms involved. If active clearance is the primary mechanism of mtHTT release, then treatment-induced changes may represent only target engagement. To investigate the mechanism(s) of mtHTT release to CSF, we are ectopically delivering mtHTT with or without inhibitors of secretion or glymphatic clearance in the presence or absence of neuronal insult. Delineating the source and mechanism(s) of entry of CSF mtHTT protein will greatly enhance utility of this promising HD biomarker.

Disclosures: **N.S. Caron:** None. **E.D. Smith:** None. **C. Yanick:** None. **S.E. Smith:** None. **J. Song:** None. **I. Seong:** None. **B.R. Leavitt:** None. **M.R. Hayden:** None. **A.L. Southwell:** None.

Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.04

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Hereditary Disease Foundation
CHDI
NIH F32 NS81964
NIH R01 NS065874

Title: Investigating and intervening in the transcriptional coordination of autophagy and inflammation in multiple neurodegenerative diseases

Authors: *A. S. DICKEY, B. CHA, A. R. LA SPADA;
Neurol., Duke Univ., Durham, NC

Abstract: Macro-autophagy (autophagy), the major cellular mechanism for macromolecule and organelle degradation, is an evolutionarily conserved, major cellular survival mechanism as is the NFκB signaling (inflammation) system. Research so far indicates that they have engaged in a close crosstalk with each other although its detailed characterization has remained elusive. Others have found that autophagy is an important regulator of inflammatory responses. Studies indicate that NFκB signaling is enhanced during aging which could explain the appearance of a low-grade inflammatory phenotype as well as the decline in autophagy. A decline in autophagic capacity and subsequent loss of protein and organelle quality control can contribute to the

development and progression of neurodegenerative diseases. While individual components of quality control pathways and inflammation pathways have been linked to neurodegenerative diseases, the relationship between these has been difficult to sort out.
Therefore, we wanted to uncover if there was upstream regulatory coordination of these pathways as they 'appear' to act in concert to aggravate issues in multiple neurodegenerative diseases.
We found that there is transcriptional coordination between inflammation signaling and autophagy in models of Huntington's disease (HD N171-82Q), Parkinson's disease (a-synuclein transgenic, MPTP model), and Tauopathy. Additionally, it may be that the highly chronic nature of the aging process affects the regulation of autophagy by NFκB signaling in a context dependent manner; that is, impairing autophagy/protein quality control and inducing a pro-inflammatory aging phenotype. We have here evidence of a coordinated program of regulation of chronic inflammation and autophagy in each model investigated.
Thus, we strived to characterize a strategy that would potentially benefit patients from multiple disease paradigms, and found that our intervention reduced inflammation and modulated autophagy to restore protein quality control in mouse models of Huntington's disease and Parkinson's disease. Efforts are underway to determine if these results extend to other disorders including ALS, and SCA7.

Disclosures: **A.S. Dickey:** None. **B. Cha:** None. **A.R. La Spada:** None.

Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.05

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Huntingtin facilitates the retrograde movement of a Rab7-containing late endosomal cargo in axons

Authors: *T. J. KRZYSTEK, J. A. WHITE, II, L. THURSTON, H. HOFFMAR-GLENNON, Y. LI, S. GUNAWARDENA;
Biol. Sci., Univ. at Buffalo, Buffalo, NY

Abstract: We previously showed that Huntingtin (HTT), the Huntington's disease protein, mediates the retrograde axonal motility of Rab7-containing vesicles and that HTT and Rab7 co-migrate within larval axons *in vivo*. Since Rab7 directs the motility of late endosomes (LEs) and autophagosomes (APs), and HTT has been previously implicated in autophagy, we hypothesize that the co-migrating HTT and Rab7 vesicles are LEs, APs, or both. In addition to Kinesin and Dynein, we found that genetic reductions of Rab-Interacting-Lysosomal Protein (dRILP),

Huntingtin-Interacting-Protein-1 (HIP1), and Rab11-interacting-protein (dRIP11) all disrupted the axonal movement of HTT or Rab7 vesicles. Immunoprecipitated Rab7 vesicle membranes contained HTT, Dynein, Dynactin, Kinesin, Rab11Fip5 (mammalian dRIP11), Hip1, RILP, LAMP, SYX17, but not Synaptotagmin or ATG5, indicating that the HTT-Rab7 vesicle complex likely does not contain synaptic proteins. Using discrete markers for specific stages of autophagy, we found that Rab7 pervades autophagy, while HTT was only found on LAMP-positive vesicles. Further, mutant syntaxin17 (SYX17), which mediates fusion between LEs and APs, disrupted the axon motility of HTT, Rab7, and LAMP. Since APs are thought to require fusion with LEs for motility in axons, and since HTT motility is influenced by SYX17, not ATG5, we propose that HTT likely co-migrates with Rab7 within axons on a Late Endosome.

Disclosures: **T.J. Krzystek:** None. **J.A. White:** None. **L. Thurston:** None. **H. Hoffmar-Glennon:** None. **Y. Li:** None. **S. Gunawardena:** None.

Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.06

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NINDS 1R01NS102486-01
NINDS R24 201603716
Stewart and Dake's Family Foundation
Help4HD
TeamKJ
Roberson Foundation
WeHaveAFace.org

Title: The use of DNA-binding domains to selectively alter Huntingtin expression in human cells and transgenic mouse models of HD

Authors: *K. D. FINK[1], P. DENG[2], J. A. HALMAI[1], J. WALDO[3], D. CAMERON[3], J. L. CARTER[5], S. DEL CAMPO[3], K. THONGPHANH[3], C. GONZALEZ[3], F. BUCHANAN[3], I. M. SANDOVAL[6], F. P. MANFREDSSON[7], J. A. NOLTA[3], D. SEGAL[4];
[1]UC Davis Med. Ctr., Sacramento, CA; [2]Inst. for Regenerative Cures, UC Davis, Sacramento, CA; [3]Inst. for Regenerative Cures, Univ. of California, Davis, Sacramento, CA; [4]Genome Ctr., Univ. of California, Davis, Davis, CA; [5]Inst. for Regenerative Cures, Univ. of California Davis, Sacramento, CA; [6]Translational Sci. and Mol. Med., [7]Michigan State Univ., Grand Rapids, MI

Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by the presence of a misfolded mutant *Huntingtin* (muHTT) protein. Reduction of HTT is an attractive therapeutic approach; however one must take into consideration the role of the normal, non-expanded version of *Huntingtin.* An ideal therapeutic would be able to selectively silence only the expanded allele, affect a large population of striatal neurons, and have a durable effect. Our lab is focused on optimizing a strategy utilizing DNA-binding domains such as Transcription Activator-like Effectors (TALE) and CRISPR/dCas9 to create transcriptional or epigenetic silencing preferentially on the mutant allele. In previous work, we have demonstrated the ability of a TALE fused to KRAB to reduce *HTT* expression in both patient fibroblast and in the brain of transgenic mice following intracranial injection of AAV-TALE. This study also demonstrated the ability of AAV-TALE to prevent some of the motor deficits associated with this model and had a significant attenuation of striatal atrophy as compared to untreated transgenic mice. While promising, the result of this study also suggested only a mild decrease in huntingtin expression in the brain at 90-days post injection likely due to a diminished potency and limited distribution of the AAV. To this end, the lab has developed a library of guide RNA for polymorphisms that exist in the promoter or regulatory region of *HTT*. These guide RNAs are being paired with a novel dCas9 variant, dxiCas9 that allows for broad PAM site recognition and the rapid evaluation of multiple effector domains. Preliminary findings suggest that dxiCas9 fused with repressive domains can significantly suppress total huntingtin expression. Current evaluations are ongoing evaluating and optimizing the preferential binding to the mutant allele. Identification of a potent DNA-binding domain that results in preferential downregulation of mutHTT that can be delivered throughout the brain would provide a platform in which therapeutic efficacy could be explored.

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Nanosymposium

016. Emerging Insights in Huntington's Disease Research: Pathological Mechanisms and Therapeutic Approaches

Location: Room S405

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 016.07

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI Grant A-11682

Title: Probing the pathological chromatin and transcriptional networks in the striatum of Huntington's disease knock-in mice

Authors: *N. WANG[1], Y. QIN[2], L. YANG[1], P. LANGFELDER[1], M. STRICOS[1], J. B. RICHMAN[1], F. GAO[2], X. GU[1], T. VOGT[3], J. AARONSON[3], J. ROSINSKI[3], G. COPPOLA[2], S. HORVATH[2], X. YANG[1];
[1]Ctr. for Neurobehavioral Genetics, Semel Inst. of Neurosci. and Human Behavior, UCLA, LOS ANGELES, CA; [2]Dept. of Human Genetics, David Geffen Sch. of Med., UCLA, Los Angeles, CA; [3]CHDI Foundation/CHDI Mgmt. Inc., Princeton, NJ

Abstract: Huntington's disease (HD) is a neurodegenerative disorder caused by a CAG repeat expansion encoding a polyglutamine repeat in mutant Huntingtin. Systems biology has offered a powerful tool to elucidate novel molecular networks dysregulated in HD. We have previously used large-scale RNA-sequencing and proteomics to study an allelic series of HD knock-in (KI) mice and identified mutant Huntingtin (mHtt) CAG-length dependent co-expression gene networks. To elucidate the causal regulatory interactions underlying transcriptionopathy in HD mice, we apply transposase-accessible chromatin with high-throughput sequencing (ATAC-Seq) to profile genome-wide open chromatin regions in medium spiny neurons (MSNs) from the adult striatum of wildtype and mHtt Q140 knock-in mice. We identify a large number of high-resolution open chromatin elements that are differentially present in HD MSNs compared to WT MSNs. We identify transcription factors (TFs) predicted to bind to the differentially accessible elements and adjacent genes that are dysregulated in a mHtt-CAG-length dependent manner, uncovering some of the underlying regulatory logic of mHtt-induced transcriptional dysregulation. Finally, we begin genetically testing top candidate transcription and chromatin factors that are dysregulated by mHtt at mRNA and/or chromatin levels for their role in modifying the transcriptionopathy in HD mice.

Disclosures: **N. Wang:** None. **Y. Qin:** None. **L. Yang:** None. **P. Langfelder:** None. **M. Stricos:** None. **J.B. Richman:** None. **F. Gao:** None. **X. Gu:** None. **T. Vogt:** None. **J. Aaronson:** None. **J. Rosinski:** None. **G. Coppola:** None. **S. Horvath:** None. **X. Yang:** None.

Nanosymposium

017. Activity Correlations and Coding

Location: Room S402

Time: Saturday, October 19, 2019, 1:00 PM - 3:00 PM

Presentation Number: 017.01

Topic: D.07. Vision

Support: MRC (UK) Grant MR/K014382/1
Wellcome Trust (UK) 101092/Z/13/Z

Title: Correlated neuronal activity in populations of visual cortical neurons potentially limits the encoding and behavioural discrimination of binocular stereoscopic depth

Authors: *A. J. PARKER[1], J. E. SMITH[2];
[2]Dept. of Phys., Anat. & Gen., [1]Univ. of Oxford, Oxford, United Kingdom

Abstract: Limits on the encoding and discrimination of sensory information arise not just from the variability of neuronal firing but also the structure of correlated firing within task-relevant neurons. Theoretical analysis suggests that sensory encoding and discrimination by the neuronal population should be limited by correlations linked to the product of the differentials of the neuronal tuning curves. We sought to build on these findings by measuring the structure of correlated firing in visual areas V1 and V4 of awake behaving macaque monkeys that were responding behaviourally to the sensory information encoded by the recorded neurons. Animals performed a binocular depth discrimination task, initially fixating a small point whilst viewing an array of four dynamic, random dot stereograms. Initially, all stereograms had identical depth, but at the trial's end one pattern changed, presenting a detection task for the animal. Utah array electrodes with 64 channels were implanted in two visual areas, yielding 195 neuron recordings for analysis in V1 and 232 in V4. We measured the pairwise interactions between neuronal recordings, based on R(signal)—correlation between the stimulus-driven responses—and R(noise)—the degree of common fluctuation in neuronal firing. In both V1 and V4, R(noise) declined as the receptive fields were more spatially separated, but R(noise) increased with R(signal). However, R(noise) was more strongly related to R(signal) in V4 than in V1. We examined the time-dependency, using a normalized integral of the paired spike-train cross-correlation that converges upon spike-count correlation in the limit (r_CCG metric; Bair et al. 2001. J Neurosci 21[5]:1676-97). Paired interactions within V1 increased after the arrival of visual stimulation peaking at 20ms. By contrast, paired interactions from V4 decreased below spontaneous firing levels, when the random-dot stimuli were presented. We tested experimentally whether the recorded population contains neuronal correlations that increase with the product of the differentials of the neuronal tuning curves. We show that this form of correlation is present in both V1 and V4 populations over a range of temporal integration limits and potentially limits sensory discrimination for binocular depth.

Disclosures: **A.J. Parker:** A. Employment/Salary (full or part-time):; Oxford University and St John's College, Oxford. **J.E. Smith:** A. Employment/Salary (full or part-time):; xford University.

Nanosymposium

017. Activity Correlations and Coding

Location: Room S402

Time: Saturday, October 19, 2019, 1:00 PM - 3:00 PM

Presentation Number: 017.02

Topic: D.07. Vision

Support: NSF PHY 1806932 to MJB
NIH R24 to MJS

Title: Population activity in the primary visual cortex is organized into well-defined clusters

Authors: Q. A. LI[1], O. HERNANDEZ[2], M. J. SCHNITZER[3], *M. J. BERRY, II[1];
[1]Princeton Univ., Princeton, NJ; [2]Stanford Univ., Stanford, CA; [3]Depts. Biol. & Applied Physics, Stanford Univ. Dept. of Biol., Stanford, CA

Abstract: Fundamental to a comprehensive understanding of any neural system is the manner in which populations of neurons encode information. Across the nervous system, certain population spiking patterns are observed far more frequently than others. A hypothesis about this structure is that these collective activity patterns fall into clusters that serve as population *codewords*. Previous work has demonstrated that population neural activity in retinal ganglion cells is always organized into a discrete set of clusters (Prentice *et al., PLoS CB* 2016; Ioffe *et al., PLoS CB* 2017). To test for the generality of this design principle, we analyzed population neural activity from mouse primary visual cortex (V1).
First, we used a two-photon mesoscope for calcium imaging to record simultaneously from ~1400 neurons in layer 2/3 of mouse primary visual cortex in awake, head-fixed animals. Animals passively viewed an ensemble of images with randomly chosen Gabor functions, with the sequence of images organized into a random-repeat structure. We inferred spike times using a standard spike deconvolution algorithm. Second, we fit the probability landscape of population neural activity using a tree hidden Markov model (HMM) and performed cross-validation on the number of hidden states in the model to determine the number of clusters. Third, we used the HMM to obtain maximum a posteriori (MAP) estimation of the cluster index for each neural activity pattern at each time step. Finally, we analyzed the parameters of the HMM, the separability between clusters, and the tuning properties of these clusters.
The model was able to fit the statistics of population spiking activity with high accuracy, but could only be applied to up to ~600 cells due to sampling limitations. For sufficiently large populations ($N \sim 400$ cells), we found well-defined clusters, similar to results in the retina for smaller populations. The number of clusters increased with the number of neurons analyzed, N. Using Fisher's Linear Discriminant Analysis, we found that the clusters also become better separated with increasing N. These different clusters were formed by activity states that were readily discriminated from one another, and they encoded features of the stimulus different from individual cells.
This coding mechanism is error-robust and enables downstream unsupervised learning. Thus, exploiting this clustering structure in the visual cortex could provide insights for understanding how the cortical hierarchy enables complex feature detection.

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Nanosymposium

017. Activity Correlations and Coding

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Presentation Number: 017.03

Topic: D.07. Vision

Support: MRC (UK) Grant MR/K014382/1
Wellcome Trust (UK) 101092/Z/13/Z

Title: Rapid noise correlations that potentially impair sensory decisions about stereoscopic depth are attenuated by V1/V4 interactions

Authors: *J. E. T. SMITH, A. J. PARKER;
DPAG, Univ. of Oxford, Oxford, United Kingdom

Abstract: When a population of neurons has correlated noise, its collective ability to encode a stimulus can be reduced. However, shared noise can be cancelled out between neurons that have positively correlated noise but opposite stimulus preferences. To see whether the visual cortex can attenuate information-limiting noise correlations, we recorded simultaneously from areas V1 and V4 in two Macaca mulatta performing a binocular depth discrimination task. Animals maintained fixation as a set of dynamic, random dot stereograms was shown, after which a sensory decision was required. Recordings were made with pairs of 64-channel Utah arrays, yielding 195 V1 units, 232 V4 units, and 4598 V1/V4 pairs in total. Noise correlations (r_{noise}) were measured at different time scales, using a normalized integral of the paired spike-train cross-correlation that converges upon spike-count correlation in the limit (r_{CCG} metric; Bair et al. 2001. J Neurosci 21[5]: 1676-97). Theory suggests that information-limiting r_{noise} will be positively related to the product of differentials of the neuronal tuning curves, and cause a saturation of the information encoded by a neuronal population of increasing size. These relationships are found within populations from the same cortical area. In contrast, the mixed V1/V4 pairs had positive r_{noise} at a time scale of >100ms that was negatively related to the similarity of the stimulus preferences and also the product of differentials. This was accompanied by a convergence of information in the mixed V1/V4 population on the theoretical limit encoded by an equivalent set of decorrelated units, but only for r_{noise} of >100ms. For this long-term r_{noise}, the amount of disparity information in the V1/V4 population exceeded the additive sum of information from each sub-population. Thus, the mixed V1/V4 population shows attenuation of correlated information-limiting noise that existed at shorter time scales of 10s of ms. This was accounted for by a simple model in which weighted V1 responses were subtracted from V4 responses. When responses from oppositely-tuned units were integrated across a window >100ms in width, the subtraction of weighted V1 responses attenuated information-limiting noise in the V4 response, leading to improved V4 disparity selectivity. We conclude that the combined action of multiple cortical areas may be able to improve information transmission through the brain.

Disclosures: J.E.T. Smith: None. **A.J. Parker:** None.

Nanosymposium

017. Activity Correlations and Coding

Location: Room S402

Time: Saturday, October 19, 2019, 1:00 PM - 3:00 PM

Presentation Number: 017.04

Topic: D.07. Vision

Support: Deutsche Forschungsgemeinschaft (GRK 1589/2)

Title: The structure of the population code in V4 microcircuits shapes pair-wise interactions on different time scales

Authors: *V. KOREN[1], A. R. ANDREI[3], M. HU[4], K. H. OBERMAYER[2], V. DRAGOI[5]; [1]Neural Information Processing, [2]Technische Univ. Berlin, Berlin, Germany; [3]Dept. of Neurobio. and Anat., Univ. of Texas Med. Sch., Houston, TX; [4]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [5]Dept Neurobiol/Anat, Univ. of Texas at Houston Dept. of Neurobio. and Anat., Houston, TX

Abstract: In visual areas of primates, neurons activate in parallel while the animal is engaged in a behavioral task. We analyse parallel spike trains in V1 and V4 visual areas while the subject performs delayed match to sample task on complex natural images. Two adult male macaques (*macaca mulatta*, 7 and 11 years old) visualized two consecutive stimuli that were either the same (condition “match”) or different (condition “non-match”), while recorded with laminar arrays across the cortical depth. The goal of our study is to examine the structure of the population code and its interplay with pairwise correlations. We decoded correct choice behaviour from the activity of single neurons as well as from neural populations of simultaneously recorded units. Comparing the predictive power of the activity of single neurons with the high-dimensional model on parallel spike trains, we find that the high-dimensional read-out predicts correct choices better than an average single neuron. Utilizing decoding weights, we divide neurons in informative and uninformative, and show that informative neurons in V4, but not in V1, are more strongly synchronized and also have stronger correlations than uninformative neurons. As neurons are divided in two coding pools according to their coding preference for matching and non-matching stimuli, in V4, but not in V1, spiking synchrony and correlations within the coding pool are stronger than across coding pools. Finally, decorrelating neural activities within the coding pool increases the performance of the decoder in both brain areas, while decorrelating across pools does not affect the performance of the decoder. In summary, our analysis shows that cortical microcircuits are structured to an important degree, that the population code contains more task-relevant information than single neurons and that in V4, the structure of the population code importantly shapes pairwise correlations. We proceed by designing a biologically realistic model of the read-out of parallel spike trains, applied in single trials and in real time. We assume that the synaptic weight between the projecting and the read-out neuron reflects the role of each projecting neuron for the computation, performed at the network level. Since in the present experimental setting, the computational task is binary discrimination, we utilize weights of an optimal linear classifier. The read-out of spike trains with our method allows to discriminate the two classes of stimuli. Disentangling the superficial,

the middle and the deep layer of the cortex, we show that in both V1 and V4, superficial layers are the best for discrimination.

Disclosures: V. Koren: None. **A.R. Andrei:** None. **M. Hu:** None. **K.H. Obermayer:** None. **V. Dragoi:** None.

Nanosymposium

017. Activity Correlations and Coding

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Presentation Number: 017.05

Topic: D.07. Vision

Support: Dan and Martina Lewis Biophotonics Fellowship
Gatsby Charitable Foundation
The Fiona and Sanjay Jha Chair in Neuroscience
Canadian Institutes of Health Research
NIH Grant 5T32EY20503-5

Title: Multichannel recordings in neuroscience: New computational methods for spatiotemporal patterns during fluctuating neural dynamics

Authors: *L. E. MULLER[1,3,4,2], Z. W. DAVIS[1,2], J. H. REYNOLDS[1], T. J. SEJNOWSKI[1]; [1]Salk Inst., La Jolla, CA; [2]Equal contribution, Salk Inst., San Diego, CA; [3]Dept. of Applied Mathematics, [4]Brain and Mind Inst., Western Univ., London, ON, Canada

Abstract: With new multichannel recording technologies, neuroscientists can now record from neocortex of awake animals with both high spatial and temporal resolution. Early recordings during anesthesia revealed spontaneous and stimulus-evoked waves traveling across the cortex. While for some time these waves were thought to disappear in awake animals and during normal sleep, our recent work has revealed traveling waves in these complex activity states. In recent work, we have introduced a non-parametric, wideband, phase-based method for detecting traveling waves in noisy multichannel data. The wideband, non-frequency-resolved nature of this algorithm minimizes the waveform distortion inherent in narrowband treatments of neural signals. Further, it requires no spatial smoothing, thereby avoiding artifacts of smoothing that can be misinterpreted as waves and that can also distort estimates of wave propagation speeds, a critical observable in establishing the underlying network-level mechanisms for these phenomena. Finally, through appropriate random shuffling permutation controls, the algorithm quantifies evidence for traveling waves, as compared to the spatiotemporal patterns that would be expected to occur by chance, allowing a quantitative, moment-by-moment, and statistically rigorous test for traveling waves in high-noise multichannel data. We have applied this method to spontaneous fluctuations of neural activity in multielectrode array recordings from awake

monkeys, as they await a faint target during a detection task. We find that spontaneous fluctuations propagate across the multielectrode array, modulate spontaneous firing rates, and strongly influence the stimulus-evoked response. These results indicate that spontaneous traveling waves shape neural computations during vision and have general implications for the way we think about noise in the brain.

Disclosures: **L.E. Muller:** None. **Z.W. Davis:** None. **J.H. Reynolds:** None. **T.J. Sejnowski:** None.

Nanosymposium

017. Activity Correlations and Coding

Location: Room S402

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Topic: D.07. Vision

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Gatsby Charitable Foundation
The Fiona and Sanjay Jha Chair in Neuroscience
Canadian Institutes of Health Research
NIH Grant T32-EY020503-06
NIH Grant RO1-EY028723
NIH Grant T32-MH020002-16A

Title: Spontaneous traveling cortical waves predict perceptual sensitivity in awake, behaving marmosets

Authors: *Z. W. DAVIS[1], L. MULLER[1,2,3], J. MARTINEZ-TRUJILLO[3], T. J. SEJNOWSKI[1], J. REYNOLDS[1];
[1]Salk Inst., La Jolla, CA; [2]Dept. of Applied Mathematics, Western Univ., London, ON, Canada; [3]Robarts Res. Inst. and Brain and Mind Inst., London, ON, Canada

Abstract: Our perception of sensory information can often be unreliable. As a simple example, a faint visual stimulus may be detected at one moment, but go unnoticed when presented later under identical viewing conditions. This variability in perceptual sensitivity may be due to moment-by-moment changes in synaptic and neuromodulatory input within the cortical network. Prior studies have found these network fluctuations can take the form of traveling waves of neural activity. However, it is unclear whether these waves have any impact on cortical function in awake, behaving animals. Using spatially distributed multi-electrode arrays, we recorded neuronal responses and local field potential (LFP) fluctuations across area MT in awake, behaving marmosets (Callithrix jacchus) during a threshold visual detection task. Using a new approach to analyze the generalized phase of wideband, non-frequency-resolved signals, we can

reliably detect spontaneous traveling waves (STWs) in the ongoing dynamics of the cortex and track their trajectories with high temporal precision. We find that (1) network fluctuations are often organized into STWs that occur several times per second and propagate across the cortex in the awake monkey, (2) STWs modulate neuronal firing during spontaneous and stimulus-evoked response periods, and (3) the state of STWs before the appearance of a target is uniquely predictive of target detection. The predictive power of STWs is much stronger than the predictive power of equal amplitude LFP fluctuations occurring in the absence of STWs. These results show that STWs are a frequent phenomenon that reflect a unique cortical state where the excitability of the local population is structured across space and time. [ZD and LM contributed equally to this work].

Disclosures: Z.W. Davis: None. **L. Muller:** None. **J. Martinez-Trujillo:** None. **T.J. Sejnowski:** None. **J. Reynolds:** None.

Nanosymposium

017. Activity Correlations and Coding

Location: Room S402

Time: Saturday, October 19, 2019, 1:00 PM - 3:00 PM

Presentation Number: 017.07

Topic: D.07. Vision

Support: NSERC Grant 2019-06741

Title: Tracking noise correlation with human fMRI

Authors: *M. MUR[1,2], K. KAY[4,5], T. W. SCHMITZ[1,3];
[1]Brain and Mind Inst., [2]Dept. of Psychology, [3]Dept. of Physiol. and Pharmacol., Western Univ., London, ON, Canada; [4]Ctr. for Magnetic Resonance Res., [5]Dept. of Radiology, Univ. of Minnesota, Minneapolis, MN

Abstract: Neurons are noisy. Even to successive presentations of the same stimulus, neurons' responses vary, and this noise is often correlated between pairs of neurons. Because correlated noise does not average out when averaging responses of neurons, it can severely limit the information present in population responses to different stimuli. How then does the brain compensate for correlated noise? Monkey electrophysiology research has demonstrated that noise correlations (r-noise) are typically strongest among neurons with similar feature preferences—i.e. neurons with high signal correlation (r-signal). Directed attention reduces r-noise most strongly among neurons with high r-signal, suggesting that dynamic changes in r-noise are a fundamental mechanism by which the brain encodes and transmits information. However, nearly all current human neuroimaging research averages activity patterns and behavior across trials, rendering these potential neural coding mechanisms invisible.
Here, we analyzed an fMRI dataset (3T, 2-mm resolution, 3 human observers) in which spatially

localized stimuli are presented multiple times at different visual field locations. We used an fMRI technique known as population receptive field (pRF) modelling to characterize the location preferences of individual voxels in human visual cortex. Although each voxel—the smallest unit of fMRI measurement—contains hundreds of thousands of neurons, the spatial resolution provided by fMRI is sufficient to capture the coarse-scale structure of the retinotopic maps in which these neurons are organized. To quantify r-noise, we examined the responses of each voxel to repetitions of a given stimulus at the same location, and computed the trial-to-trial variance around the mean. Consistent with monkey electrophysiology research, we found that r-noise increased monotonically with the similarity between individual voxels' location tuning. Our results provide cross-species translational evidence in humans that correlated noise reflects the underlying topographic map of location tuning preferences in visual cortex. This work lays the methodological groundwork for examining how attention and other phenomena affect neuronal correlations in humans.

Disclosures: M. Mur: None. **K. Kay:** None. **T.W. Schmitz:** None.

Nanosymposium

017. Activity Correlations and Coding

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Time: Saturday, October 19, 2019, 1:00 PM - 3:00 PM

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Topic: D.07. Vision

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S10 RR026783 "Multichannel Transmit Frontend for 7 Tesla" WM KECK Foundation

Title: Trial-by-trial voxelwise noise correlations may enhance the fidelity of population codes in functional magnetic resonance imaging

Authors: *R.-Y. ZHANG[1], X.-X. WEI[2], K. KAY[1];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Columbia Univ., New York, NY

Abstract: Prior studies in neurophysiology have discovered that neurons that share similar tuning functions also tend to exhibit trial-by-trial correlated activity. This form of noise correlation (NC) is denoted as tuning-compatible noise correlation (TCNC) because its sign and magnitude are systematically related to the tuning similarity between two units. In computational neuroscience, NCs between neurons have been increasingly recognized as a key factor that impacts the accuracy of population codes. On the other hand, it remains unclear how NCs between voxels impact population codes in functional magnetic resonance imaging (fMRI). Most fMRI studies use multivariate pattern analysis (MVPA) to assess the accuracy of population

codes, but the relationship between voxelwise NCs and MVPA performance remains largely underexplored. Here, we combine voxel-encoding modeling and MVPA to investigate the effects of NCs on population codes. The effects of TCNCs and NCs irrelevant to tuning similarity are systematically compared in both neuronal and voxel populations. We make three major observations. First, we replicate the classical finding that TCNCs impair population codes in a standard neuronal population. Second, we find that, in contrast to neuronal TCNCs, voxelwise TCNCs do not impair and can even improve MVPA performance when TCNCs are strong or the number of voxels is large. Third, NCs irrelevant to tuning similarity always enhance MVPA performance in both neuronal and voxel populations. Besides the conventional MVPA approach, we also confirm these results using standard information-theoretic analyses in computational neuroscience. The information-theoretic analyses further reveal the discrepancy between the effects of TCNCs in neuronal and voxel populations can be explained by tuning heterogeneity and pool sizes. Taken together, our results provide a theoretical foundation to understand the effect of correlated activity on population codes in macroscopic fMRI data.

Disclosures: **R. Zhang:** None. **X. Wei:** None. **K. Kay:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.01

Topic: G.03. Emotion

Support: NIH Grant T32 DA022975
NIH Grant K08 AA023545
NIH Grant R01 AA013892

Title: How do we feel stressed? A hippocampal connectome-based predictive modeling approach

Authors: ***E. V. GOLDFARB**[1], M. D. ROSENBERG[2], D. SEO[1], R. T. CONSTABLE[2], R. SINHA[1];
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]Yale Univ., New Haven, CT

Abstract: Although the feeling of stress is ubiquitous and can differ between men and women, the neural mechanisms underlying this affective experience remain unclear. Using a validated fMRI-based sustained stress exposure paradigm (N = 60, 30 men and 30 women) and a machine learning-based predictive modeling approach, we show that stress modulated functional hippocampal connectivity throughout the brain, and these networks predicted subjective stress responses. Stressor-modulated hippocampal connectivity with regions including the hypothalamus, parahippocampal cortex, and inferior temporal gyrus predicted higher feelings of

stress, whereas connectivity with the medial frontal gyrus and cerebellar vermis predicted lower stress. In contrast, hippocampal connectivity with regions including the putamen and periaqueductal gray differentially predicted feelings of stress for men and women. Networks were consistent across subjective stress dimensions and hippocampal subregions. These results demonstrate that hippocampal networks play a significant role in the feeling of stress and provide a novel approach for relating hypothesis-driven functional connectivity networks to clinically significant behavior.

Disclosures: E.V. Goldfarb: None. **M.D. Rosenberg:** None. **D. Seo:** None. **R.T. Constable:** None. **R. Sinha:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.02

Topic: G.03. Emotion

Support: R00MH106719

Title: The effect of rewarded extinction on implicit and explicit threat memory

Authors: *J. E. DUNSMOOR, N. E. KELLER;
UT-Austin, Austin, TX

Abstract: Defensive behaviors that result from fear conditioning can be extinguished by repeatedly presenting a conditioned stimulus (CS) without its previously paired aversive unconditioned stimulus (US). However, extinction is often followed by the re-emergence of extinguished behavior suggesting that extinction forms a secondary memory of safety that competes with the original fear memory. Previous human fear conditioning studies show that conditioning selectively enhances long-term explicit (episodic memory) and implicit memory (skin conductance response) for conditioned exemplars (Dunsmoor et al., 2018; Dunsmoor et al., 2015). In the present study, we examined whether aversive-to-appetitive counterconditioning diminishes the return of fear responses (SCR) relative to standard extinction. Moreover, we tested recognition memory for CSs that had undergone standard versus rewarded extinction. Participants were presented with a heterogeneous collection of pictures of animals, tools, and food. Exemplars from two categories (CS+; i.e., animals and tools, counterbalanced) were reinforced with an electrical shock, whereas objects from another other category (CS-; i.e., food) were never reinforced. Immediately after fear conditioning, subjects underwent extinction, in which the shock was omitted. For one CS+ category (e.g., animals) the shock was simply omitted; for the other CS+ category (e.g., tools), the shock was omitted and replaced with a positive picture. Subjects returned 24-hours later for a test of spontaneous recovery (implicit

memory) with novel CSs, and then completed a surprise recognition memory test (explicit memory) for exemplars encoded the previous day. Results from 20 healthy adults showed diminished recovery of SCRs for novel CSs from the CS+ category that had been extinguished with reward the previous day. Interestingly, participants also recognized more CS+ exemplars that had been paired with reward, relative to CS+ items that had undergone standard extinction. We suggest that rewarded fear extinction enhances explicit memory for extinction, which in turn promotes implicit extinction retrieval at test, thereby diminishing the return of fear.

Disclosures: J.E. Dunsmoor: None. **N.E. Keller:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.03

Topic: G.03. Emotion

Support: NIH NCATS Award 1TL1TR0002386-01
NIMH P50 grant MH079513

Title: Ventral hippocampal neurons show prefrontal target specificity to mediate the active inhibition of threat responding

Authors: *H. C. MEYER, F. S. LEE;
Weill Cornell Med., New York, NY

Abstract: Evidence-based interventions (e.g., cognitive-behavioral therapy) for anxiety disorders primarily rely on mechanisms of fear extinction. However, up to 50% of clinically anxious individuals do not respond to current evidence-based treatment, suggesting a critical need to optimize interventions based on the neurobiology of fear reduction. Using fiber photometry in mice, our laboratory has investigated how the ventral hippocampus may prime responding during conditions of threat and safety. Within the ventral hippocampus, neurons projecting to the prelimbic cortex, but not infralimbic cortex or basolateral amygdala, exhibit elevated activity during both safety recall and the conditioned inhibition of threat behavior but lower activity during fear recall relative to safety. In addition, the magnitude of activity in prelimbic-projecting neurons is predictive of freezing, indicating a driving role in mediating threat behavior. Distinct time courses of neural activity are also apparent during fear recall, safety recall, and conditioned inhibition, and the extent to which fear is successfully regulated (indicated by overall freezing behavior) correlates with fluorescent signal dynamics across the duration of a stimulus. Together, our findings inform the role of the ventral hippocampus in the generation and inhibition of threat response patterns, and indicate an extension of the role of ventral hippocampal modulation of prelimbic cortex to include the conditioned inhibition of fear.

Disclosures: **H.C. Meyer:** None. **F.S. Lee:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.04

Topic: G.03. Emotion

Title: The affective benefit of experiential diversity and its neural mechanisms

Authors: *A. S. HELLER[1], T. C. SHI[2], C. EZIE[3], T. R. RENEAU[1], N. M. SARAGOSA-HARRIS[3], C. J. GIBBONS[1], C. A. HARTLEY[4];
[1]Univ. of Miami, Coral Gables, FL; [2]Columbia Univ., New York, NY; [4]Psychology, [3]New York Univ., New York, NY

Abstract: Laboratory studies in animal models indicate that diversity in one's daily experience has sustained benefits for affective well-being. However, studies have not objectively examined how diversity in humans' everyday real-world experiences influences their affective state. In this talk, I will present data from studies using geolocation tracking, affective experience sampling, and in vivo neuroimaging that link day-to-day increases in the variability of an individual's physical location to increases in positive affect. We identify neural correlates of this affective sensitivity to diversity in real-world experience and examine developmental variation in this effect.

Disclosures: **A.S. Heller:** None. **T.C. Shi:** None. **C. Ezie:** None. **T.R. Reneau:** None. **N.M. Saragosa-Harris:** None. **C.J. Gibbons:** None. **C.A. Hartley:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.05

Topic: G.03. Emotion

Support: James S. McDonnell Foundation

Title: Enhancing extinction with a cognitively demanding task

Authors: *L. D. DE VOOGD[1], B. LLOYD[1], E. A. PHELPS[2];
[1]New York Univ., New York, NY; [2]Harvard Univ., Cambridge, MA

Abstract: Anxiety-related disorders are the most prevalent among all psychiatric disorders, and a primary treatment is exposure therapy, which is based on the principles of extinction. Improving extinction learning is therefore essential to optimize psychotherapy for persistent anxiety-related disorders. Recent findings in animal models and humans show that extinction learning can be improved with a cognitively demanding eye-movement intervention embedded during safety/extinction learning by triggering transient suppression of the amygdala. It is, however, unclear whether [1] any cognitively-demanding task can enhance extinction, and [2] the effectiveness of such an intervention can be enhanced by increasing cognitive load. In a three-group, between-subjects design (Experiment 1), participants completed an established Pavlovian fear acquisition/extinction/recall paradigm across two days. On day 1, one group underwent standard extinction (No-Load), a second group underwent extinction paired with a one-back working memory task (Low-Load), and a third group underwent extinction paired with a two-back working memory task (High-Load). The working memory task was presented following the CS onset for a period of 15 sec. In a two-group between-subjects design (Experiment 2), participants completed the same paradigm while undergoing functional MRI. One group underwent regular extinction (No-Load) and a second group underwent extinction together with a two-back working memory task (High-Load). In Experiment 1, we verified that performance on the two-back working memory task was more cognitively demanding than the one-back working memory task, as evinced by a lower accuracy (M=79.8% versus M=98.2%) and slower reactions times (M=652ms versus M=566ms) in the High-Load group versus the Low-Load group. Moreover, we found that differential skin-conductance responses during Re-Extinction on day 2 (i.e., when no working memory task was conducted) across all trials were reduced in the High-Load group compared to both the Low-Load and No-Load groups. This suggests that a working memory task embedded during safety learning can reduce fear responses in line with previous findings. Moreover, such an intervention seems to only be effective when the demand of the working memory task is high. This research contributes to our understanding of how cognitive load could potentially enhance extinction-based psychotherapy.

Disclosures: L.D. de Voogd: None. **B. Lloyd:** None. **E.A. Phelps:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.06

Topic: G.03. Emotion

Support: K01 MH111991

Title: Hippocampus guides adaptive choice following single-shot learning

Authors: *V. P. MURTY[1], D. F. MONTEZ[2], E. A. PHELPS[3], L. DAVACHI[4], O. FELDMANHALL[5];
[1]Temple Univ., Philadelphia, PA; [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [3]Harvard Univ., Cambridge, MA; [4]Columbia, New York, NY; [5]Brown Univ., Providence, RI

Abstract: A hallmark of human cognition is the ability to make adaptive decisions based on information garnered from limited prior experiences. Despite this, most work probes the neurobehavioral mechanisms supporting value-based choice across many experiences rather than a single episode. Using an interactive social task in which individuals make decisions to either approach or avoid players who were previously fair or unfair to them, we find that episodic memory systems centered on the hippocampus support adaptive choice. Behaviorally, we found that individuals only make adaptive choices when they have intact episodic memory of the prior social exchange with fair and unfair players. Neurally, we find that the hippocampus—rather than the striatum—shows differences when individuals make adaptive versus maladaptive choices based on these limited prior experiences ($p<0.05$, small-volume corrected). Timeseries analysis reveals that these adaptive choices elicit an initial trace signal evocative of repetition suppression signals. The extent to which the hippocampal signal was suppressed further predicts an individual's capacity to make adaptive choices (e.g., adaptive suppression, $p<0.05$). We also observed a late onset enhancement signal, consistent with the hippocampus leveraging previously executed adaptive choices to solidify a reliable neural signature for future adaptive decisions ($p<0.01$). Together these findings point to the hippocampus playing a dynamic and multifaceted role in guiding value-based choice during single shot learning.

Disclosures: V.P. Murty: None. **D.F. Montez:** None. **E.A. Phelps:** None. **L. Davachi:** None. **O. Feldmanhall:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.07

Topic: G.03. Emotion

Support: DARPA W911NF1010093

Title: The role of inflammatory processes in the ventral hippocampus in mediating stress vulnerability

Authors: *J. PEARSON-LEARY[1], S. BHATNAGAR[2];
[1]Children's Hosp. Of Philadelphia, Philadelphia, PA; [2]Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: The effects of chronic stress are diverse, and include an increased risk for depression and anxiety. A large body of research has identified a large-scale brain circuit involved in these stress-related mood disorders, including the medial prefrontal cortex and amygdala. More recently, the ventral hippocampus has been shown to be especially important for the manifestation of these stress-related mood disorders. Elevated central and peripheral inflammatory processes have been linked to stress-related mood disorders. We previously showed that male Sprague Dawley rats vulnerable to the effects of social defeat stress have elevated markers for inflammatory processes in the ventral hippocampus, including increased Iba1 density and elevated pro-inflammatory cytokine expression. We also showed increased FosB staining in the ventral hippocampus, suggesting increased neuronal activity. Finally, we showed that vascular plasticity, which is activated by inflammatory processes in adult animals, was increased in the ventral hippocampus of stress vulnerable rats. These data led us to testing the hypothesis that inflammatory processes in the ventral hippocampus could specifically promote stress vulnerability. We show that central administration of the pro-inflammatory cytokines VEGF and interleukin-1α promotes stress vulnerability, while blocking inflammatory processes in stress vulnerable rats reduces stress vulnerability. We then demonstrate that the immune-modulating microbiota *Clostridia* are associated with increased stress vulnerability, and that administering microbiota from stress vulnerable to naïve rats can promote stress vulnerability and increase inflammatory processes in the ventral hippocampus. While these data collectively identify increased neuronal activity, increased vascular remodeling, and increased inflammatory processes in the ventral hippocampus as hallmarks of stress vulnerable rats, the time-course, order, and relationship between for these processes remain unclear. Current work is underway to test the hypothesis that inflammatory processes in stress vulnerable rats promotes vascular plasticity in the ventral hippocampus to facilitate increased neuronal activity, which drives elevated anxiety-like behaviors in stress vulnerable rats. Collectively, these data increase our understanding of the role the ventral hippocampus plays in stress vulnerability, and furthers our understanding of the specific contribution inflammatory processes may play in regulating ventral hippocampus function.

Disclosures: **J. Pearson-Leary:** None. **S. Bhatnagar:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.08

Topic: G.03. Emotion

Support: Hoper for Depression Research Foundation

Title: Role of the ventral hippocampal circuit in generating and regulating cognitive responses to stress and a novel antidepressant

Authors: *C. NASCA[1], J. DOBBIN[1], B. BIGIO[2], D. MILLER[3], A. A. MATHE[4], R. HEN[5], N. L. RASGON[6], B. S. MCEWEN[2];
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Abstract: The ventral hippocampal circuit has emerged as a target for the responses to stress and antidepressant action, including the rapid actions of the novel glutamatergic agent acetyl-L-carnitine (LAC). Previous research has shown that chronic stress causes both a mineralocorticoid-dependent glutamatergic dysfunction in the ventral dentate gyrus (vDG), own to altered signaling of mGlu2 receptor (a target of LAC), and aberrant structural plasticity of ventral hippocampal pyramidal neurons (a substrate for cognitive functions). However, the circuit level mechanism underlying these effects remains to be determined. Here, we used a chemogenetic, morphological and pharmacological approach to test a role for a ventral hippocampal indirect circuitfrom the dentate gyrus to the CA1 at the chronic restraint stress (CRS) paradigm in these effects. To do this, we utilized a transgenic mouse model expressing Cre recombinase under the control of the mouse calcium/calmodulin-dependent protein kinase II alpha (Camk2a) promoter (Camk2a-Cre+ mice). Our new data suggest that 21-days of CRS leads to retraction of dendrites in vCA1 pyramidal neurons and cognitive deficits at the Y-maze test in Camk2a-Cre+ mice. Administration of the modulator of glutamatergic function LAC, for three days before the end of the CRS paradigm, ameliorated CRS-induced structural and cognitive deficits. Moreover, we found that chemogenetic silencing of neuronal firing of vCA1 pyramidal neurons receiving indirect projections from vDG glutamatergic neurons recapitulated the effects of CRS in Camk2a-Cre+ mice, and blocks the action of LAC on amelioration of the deficits at the Y-maze test in Camk2a-Cre+ mice undergoing the CRS paradigm. The findings suggest that an indirect glutamatergic circuit from the vDG to vCA1 pyramidal neurons plays a critical role in generating the responses to chronic stress, while also modulating the rapid actions of the novel glutamatergic agent LAC. Future studies are needed to delineate a possible feedback loop across the dorso-ventral hippocampal areas in the effects of stress on cognitive functions.

Disclosures: C. Nasca: None. **J. Dobbin:** None. **B. Bigio:** None. **D. Miller:** None. **A.A. Mathe:** None. **N.L. Rasgon:** None. **B.S. McEwen:** None. **R. Hen:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.09

Topic: G.03. Emotion

Support: ARO Grant 10006070

Title: The dynamic interplay between episodic memory and reward signals during reinforcement learning

Authors: *N. ROUHANI, Y. NIV;
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Dopamine-dependent plasticity in the hippocampus suggests that episodic memories may be influenced by dopaminergic reward learning signals. Of special interest are reward prediction errors, which track the difference between expected and actual rewards. Dopamine released from the midbrain is thought to convey a signed reward prediction-error signal, increasing when outcomes are better than expected and decreasing when they are worse than expected. More recently, the noradrenergic locus coeruleus, which is associated with surprising or unsigned prediction errors, has been found to co-release dopamine along with norepinephrine, highlighting a new source of hippocampal dopamine. In three experiments, we investigated how these signed and unsigned reward prediction errors influence memory as a function of learning. Participants learned through trial and error the values of objects in contexts characterized by high or low reward variance. Critically, on each trial, two trial-unique images were presented to the participant, one serving as the cue and the other alongside the reward outcome. After a short delay, participants were tested for their episodic memory of these images. We found that cue images associated with higher expected value (i.e., later in learning) were remembered better in easier, low variance environments. This suggests an effect of dopamine-mediated value learning on enhancing memory. On the other hand, in high-variance environments, memory for the image accompanying the reward outcome was modulated by unsigned reward prediction errors. That is, images associated with outcomes that were more surprising (regardless of whether the surprise was positive or negative) were better remembered. These two distinct modulations of episodic memory for events experienced when expecting and obtaining an outcome therefore map onto putatively different neural signals. We are exploring these signals using fMRI where our goal is to map the circuitry mediating the interaction between reward learning and hippocampal memory formation.

Disclosures: **N. Rouhani:** None. **Y. Niv:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.10

Topic: G.03. Emotion

Title: Modular segregation and integration of functional brain networks of emotion

Authors: *R. DAN[1,3], M. WEINSTOCK[2], G. GOELMAN[3];
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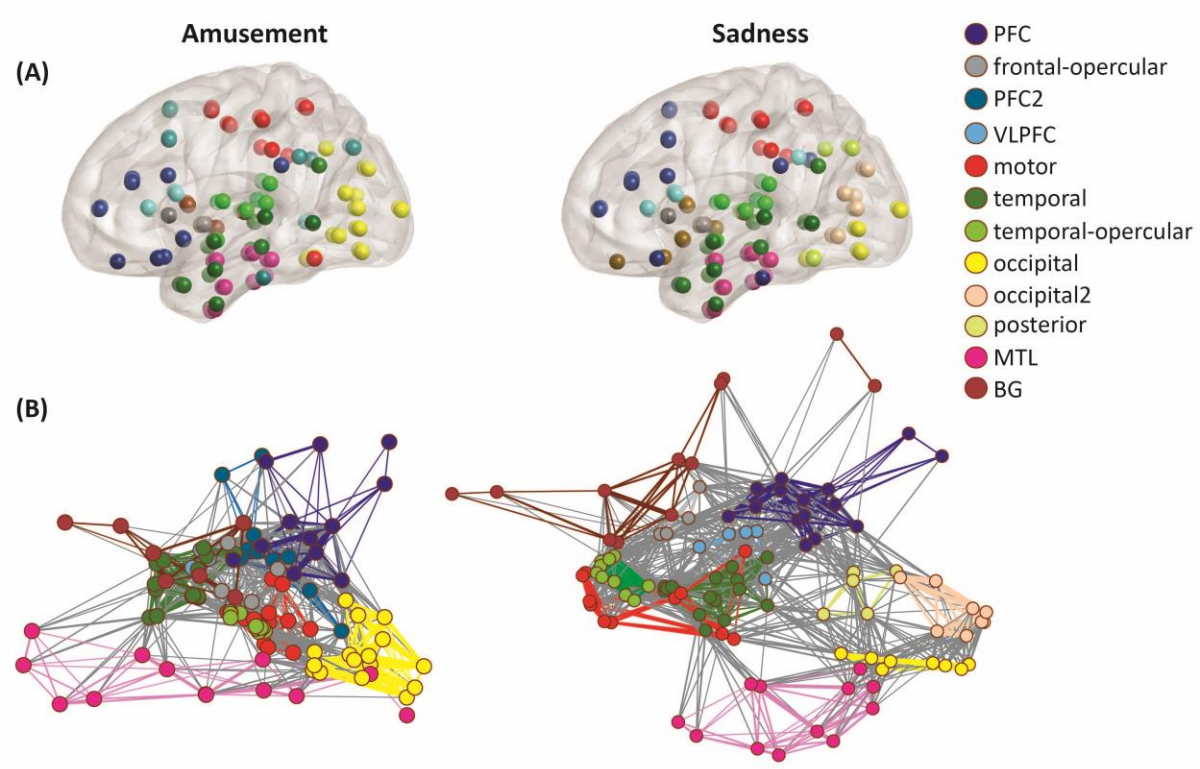
Abstract: How emotion is encoded in the human brain remains a central unresolved question. Here, we aimed to define the brain's modular organization of specific emotions: sadness and amusement, and quantify differences between these emotions in the functional segregation and integration of network communities. Fifty healthy subjects (30 women, 20 men) underwent functional MRI scans during an emotion experience experiment using continuous exposure to sad (10 minutes) and amusing (10 minutes) film clips. A graph-theoretical framework was applied to identify the community structure for each emotion, using consensus clustering and Louvian modularity on weighted positive graphs. The similarity between subjects in the modular decomposition of each emotional state was quantified using normalized mutual information. For each module and emotion, the system segregation, participation coefficient and strength of functional connectivity between pairs of modules were computed. Sadness exhibited a greater similarity in the subjects' community structure than did amusement. During amusement, increased system integration was found, quantified by the participation coefficient, specifically for prefrontal and basal-ganglia modules. Conversely, sadness was associated with increased segregation of opercular and limbic modules. Furthermore, amusement was characterized by increased prefrontal-subcortical between-module connectivity in contrast to increased prefrontal-prefrontal and prefrontal-temporal between-module connectivity in sadness. These measures of network segregation and integration were related to the subjective behavioral ratings of the intensity of the experienced emotion. Our results are the first to indicate that emotions are represented by reconfiguration of large-scale functional brain networks, with overall greater integration in amusement and segregation in sadness. These findings contribute new insights to the functional architecture of emotions in the human brain and may shed light on the pathophysiology of emotional disorders.



Network communities for each emotion. Communities (modules) are denoted by colors, and shown for amusement (left) and sadness (right). **(A)** Brain space representation of the network communities: regions are indicated by circles. **(B)** Force-directed layout of the networks using Fruchterman-Reingold algorithm. In this layout, connections act as spring-like attractive forces to position nodes in space such that nodes with more shared connections are pulled closer together. For visualization purposes, the networks are displayed at density of 0.2, i.e. the top 20% of connections are shown for each emotion.

Disclosures: **R. Dan:** None. **M. Weinstock:** None. **G. Goelman:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

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Presentation Number: 018.11

Topic: G.03. Emotion

Support: NIH R01 MH085974 (A.G.C.)

Title: Endocannabinoid signaling modulates hippocampal-evoked feed-forward inhibition in the prefrontal cortex

Authors: *X. LIU[1], J. DIMIDSCHSTEIN[3], G. J. FISHELL[4], A. G. CARTER[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY; [3]Neurobio., Broad Inst., Boston, MA;
[4]Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Projections from the ventral hippocampus (vHPC) to prefrontal cortex (PFC) play an important role in cognitive and emotional control. The activity and function of the PFC are regulated by local inhibitory networks, disruption of which leads to mental health disorders. However, little is known about how the vHPC engages inhibitory networks in the PFC or how prefrontal inhibition is modulated. Here we use optogenetics, whole-cell recordings, and intersectional viral strategies to study the vHPC-evoked feed-forward inhibition (FFI) in the mouse PFC. We first show that parvalbumin (PV+), somatostatin (SOM+) and cholecystokinin (CCK+) interneurons are present in the infralimbic (IL) PFC. We then demonstrate how PV+, SOM+ and CCK+ interneurons are differentially targeted and activated by vHPC inputs. We find that CCK+ interneurons receive strong vHPC input, and also synapse on a subset of pyramidal cells. Interestingly, we find that both direct CCK+ inputs and vHPC-evoked FFI on these pyramidal cells undergo pronounced depolarization-induced suppression of inhibition (DSI) mediated by endocannabinoids. Together, our findings reveal how vHPC inputs directly engage defined populations of interneurons in the PFC. These results underline the surprising importance of CCK+ interneurons and endocannabinoid modulation in communication between the vHPC and PFC.

Disclosures: X. Liu: None. **A.G. Carter:** None. **G.J. Fishell:** None. **J. Dimidschstein:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

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Title: Anticipation, imagination and information seeking via mid-brain, hippocampal, and prefrontal interactions

Authors: *P. DAYAN[1], K. IIGAYA[2], T. HAUSER[3], Z. KURTH-NELSON[3], J. O'DOHERTY[2], R. DOLAN[3];
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Abstract: Humans and other animals seek information about uncertain and delayed appetitive outcomes. We used fMRI to examine the components of a recent model of information seeking in which it arises from the way that prediction errors boost savouring - the subjective utility generated by the anticipation of delayed future rewards. We found that three regions orchestrate anticipatory pleasure. We show ventromedial prefrontal cortex (vmPFC) tracks the value of anticipation; regions of the midbrain often associated with dopaminergic neuromodulation respond to the prediction errors that are suggested as enhancing anticipation, while the sustained activity in hippocampus provides for functional coupling between these regions. This coordinating role for hippocampus is consistent with its known role in the vivid imagination of future outcomes. Our findings throw new light on the neural underpinnings of how anticipation influences decision-making, while also unifying a range of phenomena associated with risk and time-delay preference.

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Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.13

Topic: H.01. Animal Cognition and Behavior

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Title: Task-dependent changes in the large-scale dynamics and necessity of cortical regions

Authors: *L. PINTO[1], K. RAJAN[1,5], B. DEPASQUALE[1], S. THIBERGE[2], D. W. TANK[1,3,2], C. D. BRODY[1,4,3];
[1]Princeton Neurosci. Inst., [2]Bezos Ctr. for Neural Dynamics, [3]Dept. of Mol. Biol., [4]Howard Hughes Med. Inst., Princeton Univ., Princeton, NJ; [5]Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Neural activity in many cortical areas is correlated with perceptual decision behaviors, but inactivation studies suggest that only a small number of those areas are necessary for these behaviors. Here we show that the number of required cortical areas, and their dynamics, vary widely across tasks with different cognitive demands. We used large-scale, all-optical perturbation and recording methods to perform an unbiased survey of both the Ca^{2+} activity patterns and perturbation effects across the entire dorsal cortex while mice performed two related virtual-reality (VR) navigation tasks with different cognitive requirements. The first was an accumulation-of-evidence task in which mice were trained to hold and update accrued sensory evidence over seconds while navigating in a virtual environment. The second was a visually-guided task in the same virtual maze and with almost identical sensory stimuli, but with reward location being indicated throughout. In the visually-guided task, bilateral whole-trial inactivation of only a few visual cortical and premotor regions impaired performance. In contrast, in the evidence-accumulation task, performance was impaired by inactivation of any patch of the dorsal cortex, with diverse patterns of behavioral deficits. Widefield imaging revealed widespread ramps of Ca^{2+} activity during both tasks. Additionally, during accumulation different regions had more diverse activity profiles, leading to reduced inter-area correlations. Furthermore, within trials of the demanding task, more decorrelation between parietal and frontal cortices was associated with greater behavioral performance. These data suggest that performance of more cognitively-demanding tasks alone requires the engagement of various differing computations across widespread regions of cortex. Finally, we trained a recurrent neural network model, with cortex-inspired modular architecture, to perform both the visually-guided and the accumulation task, with fixed synaptic connectivity for both tasks. Based on this model, we argue that the more complex computation underlying evidence accrual could itself explain our imaging and inactivation findings.

Disclosures: L. Pinto: None. **K. Rajan:** None. **B. DePasquale:** None. **S. Thiberge:** None. **D.W. Tank:** None. **C.D. Brody:** None.

Nanosymposium

018. Neural Circuits, Memory, and Emotion

Location: Room S403

Time: Saturday, October 19, 2019, 1:00 PM - 4:30 PM

Presentation Number: 018.14

Topic: G.03. Emotion

Title: Impact of reward access instability on psychopathology and reward circuit neurodevelopment in children

Authors: *J. HOGEVEEN;
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Abstract: The development of adaptive decision making demands a stable reward environment, wherein future outcomes can be predicted from prior reward history. Given the potential for aberrant reward processing to drive risk for psychopathology, it is critical to know whether unstable reward environments modulate the development of reward neurocircuits in children. We leveraged unprecedented fMRI data from the first release of the *Adolescent Brain Cognitive Development* study (ABCD; N=4085 in current analyses) to determine how reward environment instability modulates psychopathology and reward circuit development in 9-10 year old children. We hypothesized that population-level indicators of reward access instability–namely, household income, food insecurity, and neighborhood socioeconomic disadvantage–would be associated with elevated levels of psychopathology, and aberrant recruitment of reward circuits during a well-validated fMRI decision making paradigm. To assess psychopathology, we analyzed internalizing and externalizing problems composite scores from the Child Behavior Checklist (CBCL). To measure reward circuit functioning, we analyzed ABCD's *Monetary Incentive Delay* (MID) task. The MID involves working to obtain potential rewards or avoid potential losses, and is a robust activator of ventral striatum (VS) and amygdala (AMY), structures that are critical to reward-guided decision making in stable and unstable environments, respectively. Results generally supported these hypotheses, and remained significant after covarying for parent marital status, age, sex, race, and study site in the models. Decreased household income, increased food insecurity, and increased neighborhood socioeconomic disadvantage were all associated with increased internalizing and externalizing problems. MID data indicated that i) increased household income predicted decreased RH-AMY recruitment during loss anticipation (p<0.001), ii) food insecurity predicted increased RH-AMY recruitment across both reward (p=0.002) and loss anticipation (p=0.014), and iii) neighborhood disadvantage predicted decreased recruitment of the VS during reward anticipation (p=0.033). To be clear, these data represent preliminary analyses of pre-packaged data using mean activation across Freesurfer-based ROIs. In future work, our lab will be re-processing the MID fMRI data in a voxelwise, whole-brain analysis. Overall, the current data suggest that reward environment instability increases both internalizing and externalizing psychopathology, and leads to aberrant recruitment of the VS and AMY during reward-guided decision making in children.

Disclosures: J. Hogeveen: None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

Location: Room S505

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 019.01

Topic: H.02. Human Cognition and Behavior

Title: The explicit and implicit in visual judgment

Authors: *K. MOGI;
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Abstract: In general, there is more information in the visual field than can be handled by the cognitive system (Block 2011). Due to the superfluous nature of visual information, there are explicit and implicit elements in the handling of visual perception. The exact nature of the division of labor between implicit and explicit systems is still debated (Lau and Ronsenthal 2011, O'Regan 2011, Brown 2012).
Number of research have indicated that the emotional system making judgements about the visual field is affected even when the cognitive system is unable to handle all the relevant information available in the visual field. In some cases, the implicitly processed information has more effect on the subjects' emotive judgments than the explicitly processed information.
Here I investigate the roles played by the explicitly and implicitly processed elements in the visual environment in the subjects' cognitive and emotional judgments. In particular, I investigate how elements in the visual field affect the subjects' affective judgments such as security, comfort, and reliability in typical situations involving natural scenes, such as those encountered while driving a car.
The subjects were required to make perceptual and cognitive judgments in an visual field flowing from the front to the back. The stimuli included houses, trees, pedestrians, etc.,, occurring frequently in the daily lives. The subjects were given alternative scenarios as to how the visual scenes were generated and presented, with varying degrees of explicit and implicit information combined.
The ratio of division of labor between implicit and explicit processing within the subject's visual systems was controlled by fine-tuning the way the visual stimuli were presented. Specifically, scenarios were presented simulating situations in self-driving cars, where various information concerning the algorithm (e.g., values of evaluation function assigned to elements related to the possible alternative maneuvers of the automobile) were either explicitly presented or absent, affecting the subjects' ethical perceptions and judgments.
Based on the results, I analyze the nature of the different roles played by explicit vs implicit information on the subjects' judgments in perceptual, cognitive, and emotive contexts.

Disclosures: K. Mogi: None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

Location: Room S505

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 019.02

Topic: H.02. Human Cognition and Behavior

Support: JSPS Grant JP16H06324

JSPS Grant JP18K13267
JST CREST Grant JPMJCR17A4-17941861

Title: Mere presence of co-forager automatically shifts human foraging tactics toward “fast and easy” food

Authors: *Y. OGURA, T. MASAMOTO, T. KAMEDA;
Dept. of Social Psychology, Univ. of Tokyo, Tokyo, Japan

Abstract: Many animal species, including humans, often engage in foraging with other individuals despite potential competition for food. To cope with competition, animals may adopt different foraging tactics in a group situation than when foraging alone. We hypothesized that in the presence of co-foragers, animals would shift their tactics from foraging less frequently for larger food amounts to more frequent reaching for smaller food amounts. Because smaller foods are generally more abundant in nature and allow faster consumption, such tactics should allow animals to ingest food more securely even if others attempt to scrounge it. Here, we demonstrated that humans, those believed to be among the most “intellectual” gregarious animals, exhibited such a shift in foraging tactics automatically, even when a co-forager was merely present but did not compete with them for food. In a laboratory setting, human participants were asked to engage in a “taste test” of potato chips paired with another participant or alone. We measured reach frequency for food and weight of potato chips per reach by using electronic balances. Participants in pairs instantaneously exhibited a systematic behavioral pattern to reach for smaller food more frequently. We also observed that the increase in reach frequency was a more robust response to social foraging than the decrease in the amount of food per reach. State-space modeling revealed that this reaching pattern was clearly distinct from the pattern that was observed in a weighing-only condition (in which participants simply weighed the same food without eating any), which indicates that the shift toward reaching smaller food more frequently is tactical behavior in a social foraging context. The automatic behavioral shift toward more frequent reach for smaller and easier food enables securer ingestion against potential scrounging attempt by other co-eaters, and may reflect common built-in foraging tactics across many gregarious animals.

Disclosures: **Y. Ogura:** None. **T. Masamoto:** None. **T. Kameda:** None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

Location: Room S505

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 019.03

Topic: H.02. Human Cognition and Behavior

Title: Supramodal cortical representation of identity

Authors: *V. S. CHAUHAN[1], S. A. NASTASE[3], A. DASH[1], Y. HALCHENKO[1], M. I. GOBBINI[2];
[1]Dept. of Psychological and Brain Sci., [2]Dartmouth Col., Hanover, NH; [3]Princeton Univ., Princeton, NJ

Abstract: Spontaneous retrieval of person knowledge is pivotal for social interaction. Not only do we need to recognize people in different environments and circumstances, we also need to integrate information about them across different modalities. Here, we used neuroimaging data from 16 participants to investigate the neural systems underlying the supramodal representation of famous identities. Previous research suggests that activity along the middle temporal gyrus and the right posterior temporal sulcus can be used to decode identity across modalities. These studies utilized highly controlled auditory and visual stimuli to study supramodal representation. We reasoned that more naturalistic stimuli would elicit activity across a wider range of cortical areas involved in representing person knowledge, such as the temporoparietal junction, posterior cingulate cortex/precuneus and medial prefrontal cortex. Our approach used a stimulus-rich design with ten highly-recognizable Hollywood celebrity identities and three different presentation modalities: video clips sampled from television interviews; sound clips containing complete phrases from interviews; and the celebrity names presented as text. Univariate results indicate stimuli from each modality elicit activity in the relevant sensory cortices. Moreover, responses to pairs of identities within single modalities were discriminable in sensory cortices. Finally, we have implemented a multivariate searchlight analysis to localize areas of the brain that encode identity-specific information in a supramodal manner.

Disclosures: V.S. Chauhan: None. **S.A. Nastase:** None. **A. Dash:** None. **Y. Halchenko:** None. **M.I. Gobbini:** None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

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Presentation Number: 019.04

Topic: H.02. Human Cognition and Behavior

Support: NIH NIMH R01 MH107513
NIH NIMH R01 MH11629
NIH NIMH R01 MH119430
NIH NIMH F30 MH116626
NIH R37 HD 090153

Title: A two-person neural mechanism for sharing social cues during real eye contact

Authors: *J. HIRSCH[1,2,3,6], J. A. NOAH[1], X. ZHANG[1], S. DRAVIDA[4,5], M. KELLEY[5]; [1]Psychiatry, [2]Neurosci., [3]Comparative Med., [4]MD/PhD Training Program, [5]Interdepartmental Neurosci. Program, Yale Sch. of Med., New Haven, CT; [6]Med. Physics and Biomed. Engin., Univ. Col. London, WC1E 6BT, UK, London, United Kingdom

Abstract: Eye-to-eye contact is widely recognized as a salient social cue for live interactive communication. Further, neurophysiological and neuroimaging evidence reveals mechanisms in the human brain that interpret highly nuanced facial expressions of which eye contact is fundamental. However, the neural processes that encode simultaneous two-person eye and face information have not been identified although the question represents an emerging theoretical frontier in social neuroscience. It has been proposed that neural coupling of signals between brains (coherence) is an indicator of shared encoding of information that is transmitted and subsequently received[1]. Previous findings from our group report neural coupling between fusiform gyrus and angular gyrus during a live and interactive face-to-face task where relevant face information is simultaneously transmitted and received[2]. Based on this context, we test the hypothesis that real and simultaneous eye-to-eye contact will be associated with cross-brain coherence between the fusiform gyrus and the angular gyrus. If so, then the findings advance a theoretical framework for a cross-brain neural system to share live and rapid eye-to-eye and face information.

In this study hemodynamic signals were acquired using a two-person neuroimaging paradigm and functional near-infrared spectroscopy (fNIRS) during either live face-to-face contact or viewing a dynamic face-video (15 dyads, n=30). Neural coupling between participants was determined by wavelet analyses that compared cross-brain correlations with wavelet kernels for signals originating from 12 brain regions (previously described[3,4]). As predicted, neural coupling between angular gyrus and fusiform gyrus was greater during the real face condition than during the video face condition ($p < 0.01$). These two coupled regions are recognized components of social[5] and face systems[6]. This neural coupling was not observed when the partners were computationally scrambled as would be expected if neural coupling represented live encoding of reciprocal and socially informative facial information. Further, no other cross brain region pairs were coherent. These findings suggest that fusiform gyrus and angular gyrus regions may serve a previously unappreciated role associated with encoding of rapidly acquired spontaneous social and facial information detected during live face-to-face interaction.

[1]Hasson, et al, Science, 2004; [2]Piva, et al, Front Hum Neurosci, 2017; [3]Hirsch, et al, Neuroimage, 2017;[4]Hirsch, et al, SCAN, 2018; [5]Carter and Huettel, Trends Cogn Sci 2013; [6]Pitcher, et al, Exp Brain Res, 2011.

Disclosures: J. Hirsch: None. **J.A. Noah:** None. **X. Zhang:** None. **S. Dravida:** None. **M. Kelley:** None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

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Topic: H.02. Human Cognition and Behavior

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Title: Dissociating neural representations of own and other cognitive mental states in human medial prefrontal cortex

Authors: *S. JIANG[1,2], S. WANG[1,2], X. WAN[1,2];
[1]Beijing Normal Univ., Beijing, China; [2]IDG/MacGovern Inst. for Brain Res., Beijing, China

Abstract: Humans are social beings. We communicate with each other by sharing our own mental states. Thereby, we should represent the others' mental states, along with our own mental states, in our brains. The representations and manipulations of the others' mental states are mentalizing, while those processes of our own mental states are metacognition. However, it remains unclear how we dissociate the neural representations of our own and the others' mental states in our brains. One of the critical mental states bridges mentalizing and metacognition is decision uncertainty (confidence), the degree of subjective belief that the decision is incorrect (correct). We often estimate the decision uncertainty from the others' performance. In this study, we compared the neural representations of one's own decision uncertainty, the other's decision uncertainty and the objective performance accuracy. In the metacognition task, immediately after the participants (n = 26) underwent a perceptual decision-making task, they reported the decision confidence to which extent the decision would be correct. In the mentalizing task, the participants reported an unknown opponent's decision confidence immediately after observing the opponent's decision-making process. In the association task, the task procedure was identical to the mentalizing task except that they reported the objective degree that the decision would be correct. Using functional magnetic resonance imaging (fMRI), we found that the dorsal anterior cingulate cortex (dACC), was selectively associated with representations of one's own decision uncertainty during the metacognition task, which was consistent with our previous study, while the dorsal medial prefrontal cortex (DMPFC) were instead associated with representations of the other's decision uncertainty during the mentalizing task. However, both regions were not associated with representations of the ones' own and the other's objective performance accuracy. Therefore, our findings suggest that two dissociable neural substrates in human MFPC in representations of one's own and other mental states about decision uncertainty.

Disclosures: **S. Jiang:** None. **X. Wan:** None. **S. Wang:** None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

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Presentation Number: 019.06

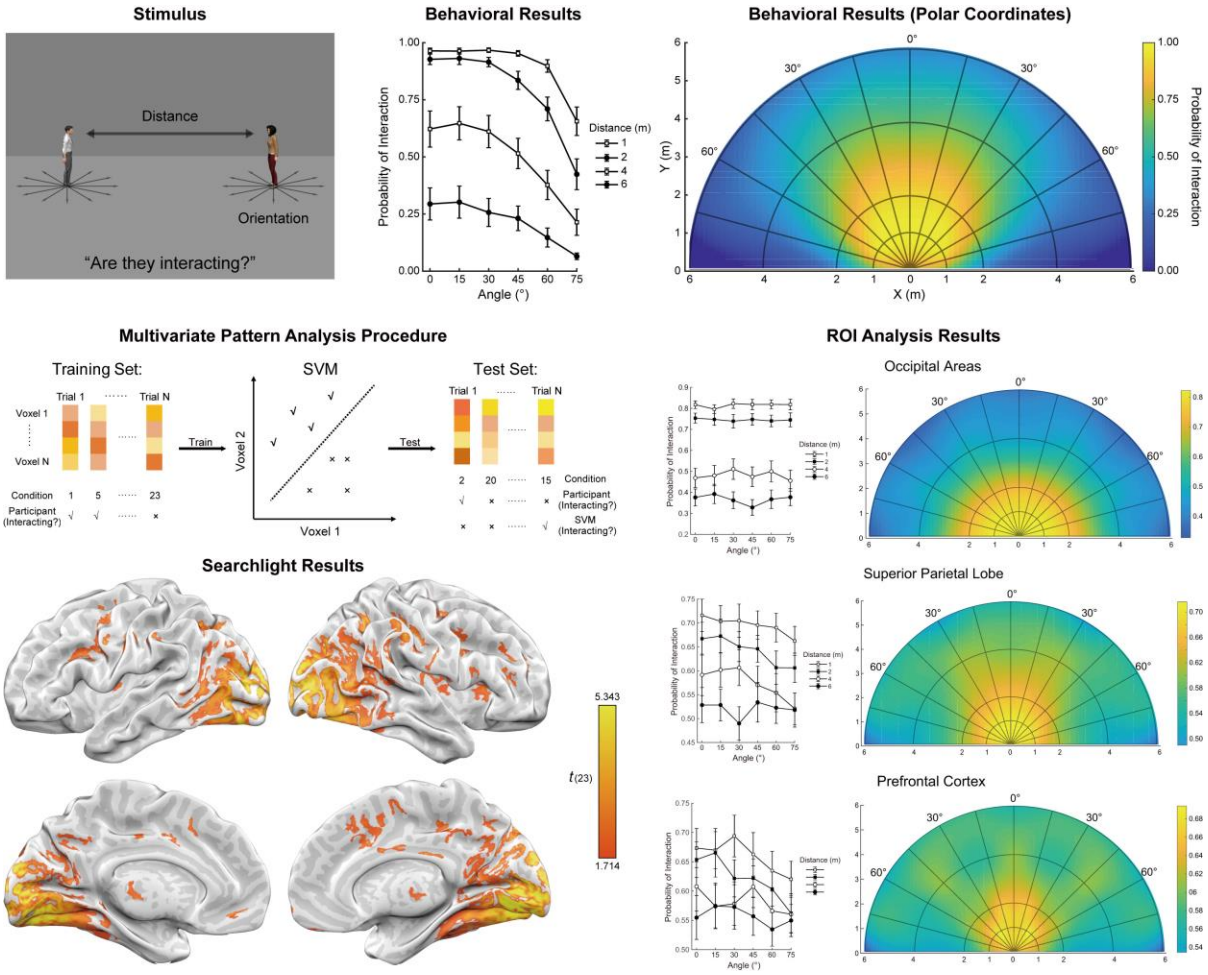
Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (Grants No. 31771209)

Title: Decoding social interaction of other people in the human brain

Authors: *Q. LIANG[1], J. LI[1], Y. LIANG[1], Z. NIE[1], S. KUAI[1,2];
[1]Sch. of Psychology and Cognitive Sci., East China Normal Univ., Shanghai, China; [2]NYU-ECNU Inst. of Brain and Cognitive Sci., New York Univ. Shanghai, Shanghai, China

Abstract: Understanding social interactions of other people is crucial for the social activities of human beings. Recent studies have indicated that the human brain utilizes spatial cues (e.g., interpersonal angle and distance) to judge the interactions of others in a social scene. Little is known about how the human brain encodes these spatial cues to form the perception of other people's social interaction. In this study, we asked participants to watch two virtual humans and judge the status of their social interaction while the brain activation was recorded in an MRI scanner. We varied the interpersonal angle from 0° to 75° and interpersonal distance from 1m to 6m, resulting in 24 stimulus conditions. In an event-related run, stimulus conditions plus a fixation condition were presented in an M-sequence. For each trial, the stimulus was presented for 1000ms followed by a 500ms blank. Participants were asked to report whether two virtual humans were interacting or not. A searchlight-based multivariate pattern analysis (MVPA) demonstrated the occipital areas, the fusiform gyrus, the posterior temporal lobe, the parietal lobe and the prefrontal cortex demonstrated significantly higher accuracies than the chance level in decoding social interaction. In each of these regions, we selected 200 strongest activated voxels to train a support vector machine (SVM) to classify the perception of social interaction. We calculated the probability of being classified as interacting by the SVM classifiers and generated probability maps of each region. Results suggested that the occipital areas and the fusiform gyrus decoded the interpersonal distance, the temporal and parietal lobe decoded both the interpersonal distance and angle, and then the frontal cortex interpreted the social interaction. These results indicate that our brain decodes the perception of others' social interaction in a coarse-to-fine fashion engaging a range of brain network.



Disclosures: **Q. Liang:** None. **J. Li:** None. **Y. Liang:** None. **Z. Nie:** None. **S. Kuai:** None.

Nanosymposium

019. Social Cognition: Behavior and Neural Mechanisms I

Location: Room S505

Time: Saturday, October 19, 2019, 1:00 PM - 2:45 PM

Presentation Number: 019.07

Topic: H.02. Human Cognition and Behavior

Support: the Key Program for International S&T Cooperation Projects of China(MOST, 2016YFE0129100)
the National Natural Science Foundation(No. 31471068)
the Fundamental Research Funds for the Central Universities(2017EYT33)

Title: Oxytocin enhances mentalizing by vicariously sharing metacognitive experience

Authors: *F. SUN[1], S. WANG[1], T. YANG[2], N. LIU[2], X. WAN[1];
[1]Beijing Normal Univ., State Key Lab. of Cognitive Neurosci. and Learning and IDG/McGovern Inst. for Brain Res., Beijing, China; [2]Chinese Acad. of Sci., State Key Lab. of Brain and Cognitive Science, Inst. of Biophysics, Beijing, China

Abstract: Oxytocin displays great enhancement of human complex social behaviors in a prosocial fashion. The underlying mechanisms, however, remain elusive. A core social cognition for human social behaviors is mentalizing, to understand other's minds. We here devised a novel experimental paradigm to dissect intrinsic representations from the external cue's associations in mentalizing others' confidence. The participant predicted an unknown partner's confidence rating in regard to this person's perceptual decision in the mentalization task and conducted the association task as a non-social control condition. Using a double-blinded, placebo-controlled within-subjects design (n = 40), we examined the oxytocin effects in regulating representations of others' confidence. We removed the components associated with the external cue (the response time) from the variances of the estimated confidence and accuracy, and calculated the respective areas under curve (AUCs) measured by the residual signals. Our results showed that the residual AUC in inference of the other's confidence became significant in the oxytocin treatment, and larger than that in the placebo treatment. But there was no such difference in inference of the machine's accuracy. These results suggest that oxytocin may induce a telepathy-like increase of mentalizing ability in predicting an unknown partner's performance, but not a machine's performance. One of the possible ways to attribute others' hidden mental states is vicariously sharing one's own experience through mental simulations of interacting with the environment. To test this hypothesis, we examined the associations between the residual AUCs in the mentalization/association task and in the metacognition task across the participants. As the participant's own residual AUC in the metacognition task was higher, the residual AUC in inference of the other's confidence became also higher than that in inference of the machine's accuracy in the oxytocin treatment. This miraculous effect was likely caused by vicariously sharing one's own metacognitive experience. Critically, this association did not originally exist in the placebo treatment. The results revealed that oxytocin enhanced vicarious sharing one's own experience in mentalizing the other's cognitive states. Hence, our findings suggest that oxytocin may specifically promote a sustained motivational state to share two minds in social interactions.

Disclosures: **F. Sun:** None. **S. Wang:** None. **T. Yang:** None. **N. Liu:** None. **X. Wan:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.01

Topic: I.04. Physiological Methods

Support: DARPA Contract N66001-17-C-4002

Title: An ultrathin flexible CMOS neural microelectrode array

Authors: *R. HUQ[1], D. TSAI[2], K. L. SHEPARD[1];
[1]Columbia Univ., New York, NY; [2]UNSW, Sydney, Australia

Abstract: Implantable silicon neural probes leveraging CMOS technology have enabled interfaces of unprecedented scale due to their ability to use integrated circuitry to multiplex among massive arrays of ultra-dense electrodes. However, the mechanical mismatch (and resultant micromotion) between traditional silicon devices and soft neural tissue has been implicated as a key driver of inflammatory responses leading to signal degradation, limiting their deployment in chronic recording applications. Here we present an approach that bridges the gap between the ultra-high density capabilities allowed by CMOS and a form factor suited for chronic implantation, by developing a process to transform rigid CMOS devices into flexible biocompatible interfaces. We do this by aggressively thinning the silicon substrate these devices rest on using a combination of mechanical grinding and polishing for bulk removal with plasma etching for stress relief. Multimodal characterization (FIB/SEM, optical and contact profilometry, and Raman spectroscopy) validates that postprocessed devices exhibited similar backside roughness and surface stress distributions to unprocessed devices. Further 3D Raman spectroscopy was utilized to quantify any subsurface damage resulting from the thinning processes. As a demonstration of this processing flow, we have thinned an ultra-dense 67 mm^2, 65,536 electrode CMOS neural array from 300 um to 10 um remaining silicon thickness (RST). Once post-processed, the array can be flexed to a diameter <5 mm with no mechanical damage. We further demonstrated that this processing results in unaltered electrical performance, comparing noise and SNR measurements taken with both thinned devices as well as unprocessed arrays. Finally, ex vivo neural recordings were performed with both sets of arrays applied to live mouse hippocampal brain slices exhibiting 4-aminopyridine-induced epileptiform activity.

Disclosures: R. Huq: None. **D. Tsai:** None. **K.L. Shepard:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.02

Topic: I.04. Physiological Methods

Support: CCDR-N agency, Norte2020 grant NORTE-01-0145-FEDER-000023

Title: High-density recording using a new concept of silicon neural probes

Authors: *A. NOVAIS, J. FERNANDES, H. FONSECA, C. CALAZA, J. GASPAR;
Micro and Nanofabrication, INL - Intl. Nanotechnology Lab., Braga, Portugal

Abstract: To understand how the brain function is the foremost goal in neuroscience research but it also carries technologic challenges to develop tools to do so. Neuroscientists have advanced significantly in the field of systems neuroscience in recent years being able to perform simultaneous recordings from increasingly large neuronal populations. The number of neurons recorded simultaneously has grown exponentially, doubling in number every approximately 7.4 years. These numbers have recently received higher impulses from the onset of Silicon (Si) probes. In order to contribute to these advances, we propose to develop an affordable fabrication process for a high-density recording Si probe. We designed to fabricate an 8 shank Si probe, with 8 microelectrodes, in a total width of ~50 µm and thickness of 15 µm, with a range of lengths (2.5, 5 and 10 mm long). Such design will allow the implantation through the *Dura matter* meninges, decreasing surgery time and risk (especially for cortical recordings). Robust Si probe can be obtained taking advantage of deposition, lithography and dry Si micro-machining techniques. Briefly, microelectrodes present on the shank tips have an area of 72 µm of a metal stack of gold and titanium tungsten, Si is passivated with alumina from the metal vias from the microelectrodes to its end (metal pads) in the base of the probe. In order to avoid wire bonding of each metal pad, a microfabrication process using polyimide (PI) on Si is used. PI with aluminum as internal metal is bonded to the Si metal pad, that ends in a PI aluminum pad array for a flexible flat cable connector insertion, which is bonded to a printed board with a connector that will connect to the pre-amplifier head stage. Dry deep reacting ion etching will be used to design Si shank probes. Breakout beams (U-shape) that connect the side of the probe to the bulk wafer will be used to allow wafer handling that will also allow an easy break with tweezers. Devices are fully characterized using several metrology techniques along the fabrication process. Herein we deliver a detailed fabrication process to obtain a 64 channel Si-probe offering multisite neuronal recording with full characterization ready for acute and chronic neural recordings of rodents brain. It is our understanding that this work will contribute to the technological development of tools for simultaneous recordings of neural populations in a more precise comprehension, adapting to systems neuroscience needs.

Disclosures: **A. Novais:** None. **C. Calaza:** None. **J. Gaspar:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.03

Topic: I.04. Physiological Methods

Support: NIH Grant 1U01NS094190-01

Title: Multi shaft and single shaft active high density neural probes based on SiNAPS technology

Authors: G. N. ANGOTZI[1], F. BOI[2], A. LECOMTE[1], *L. BERDONDINI[1];
[2]Neurosci. and Brain Technologies, [1]Fondazione Inst. Italiano di Tecnologia, Genova, Italy

Abstract: High-resolution, large-scale sensing devices capable of monitoring spiking and low frequency bioelectrical neuronal signals within and across large brain areas can nowadays be realized using CMOS technology. Different solutions to realize these active dense probes for intra-cortical neural recordings from a large number of densely packed electrodes have been recently proposed (Jun et al., 2017, Fiáth et al., 2018, De Dorigo et al., 2018, Angotzi et al., 2019). Among these, our SiNAPS probes overcome the major scaling bottleneck caused by the spatial limits of analog front-ends (Seymour et al., 2017), thus allowing on-probe multiplexing of thousands of electrode on a few output lines. Here, we present the technological concepts of SiNAPS and we report on the use of this technology to realize single-/multi-shaft active dense probes. Differently than other solutions, the SiNAPS circuit architecture is based on the Active Pixel Sensor (APS) concept (Fossum, 1997): a DC-coupled front-end circuit for signal amplification and low-pass filtering is located directly underneath each electrode-pixel contact (Berdondini et al., 2001), thus obviating the need for the large-area capacitors used in conventional AC-coupled amplifiers and enabling on-probe multiplexing. SiNAPS technology is based on the concept of groups of pixels constituting independent modules. This peculiar feature of our technology uniquely allows rapid re-designs of probe layouts and geometries for customized experimental applications. As a proof of concept, we fabricated a SiNAPS probe integrating 1024 electrode-pixels (size 26µm, pitch 28µm) arranged on four distinct shafts (80µm wide x 5mm long; incorporating 256 contacts/shaft covering 3.6mm; shaft separation 560µm). By re-using the same 32 electrode-pixels analog module we used for the previous single-shaft device (Angotzi et al., 2019), this new 4-shaft device required only 2 weeks of CMOS design, plus 40 days of fabrication from the commercial CMOS foundry. In perspective, the modularity of SINAPS can be exploited, for instance, to scale up the number of electrodes, to realize different layouts, or to reduce the cross-sectional sizes of the shafts, thus realizing a range of probes that could meet different experimental needs. Further, because the amplifier front-ends are not located on the base of the probes, our technology minimizes the total silicon area of the probes and can facilitate the development of probes adapted for chronic recordings simultaneously maintaining reasonably low the total cost per device.

Disclosures: **G.N. Angotzi:** None. **F. Boi:** None. **A. Lecomte:** None. **L. Berdondini:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.04

Topic: I.04. Physiological Methods

Support: R01NS102917
R21NS102964
W81XWH-16-10580

Title: Bridging large-scale neural recordings and nearly-cortex-wide optical acquisitions

Authors: *X. LI, Z. ZHAO, H. ZHU, F. HE, L. LUAN, C. XIE;
Univ. of Texas at Austin, Austin, TX

Abstract: Neural circuits span diverse spatial scales: they consist of nearby clusters of neurons as well as neurons distributed across multiple brain areas. Technically, electrical recording by implanted electrodes allows for millisecond resolution detection of individual neuron activity, but can typically only sample a small portion of all neurons involved in a circuit. Optical measurements of neuronal activity, in contrast, permit high spatial-resolution mapping of a large number of neurons, but typically penetrate < 1 mm in depth and have limited temporal resolution. It is therefore desired to combine the complementary advantages of optical and electrical measurements. Here we demonstrate a method that combines ultraflexible neural electrodes with nearly-cortex-wide polymer cranial window to enable large-scale recording from individual neurons and simultaneous optical imaging in the neocortex for longitudinal studies. We show that this setting flexibly allows for concurrent implementation of multiple neural recording and modulation techniques, including spatially resolved recordings at multiple regions and in deep structures, epi-fluorescence imaging across cortex, two-photon imaging at multiple cortical regions, and optogenetics.

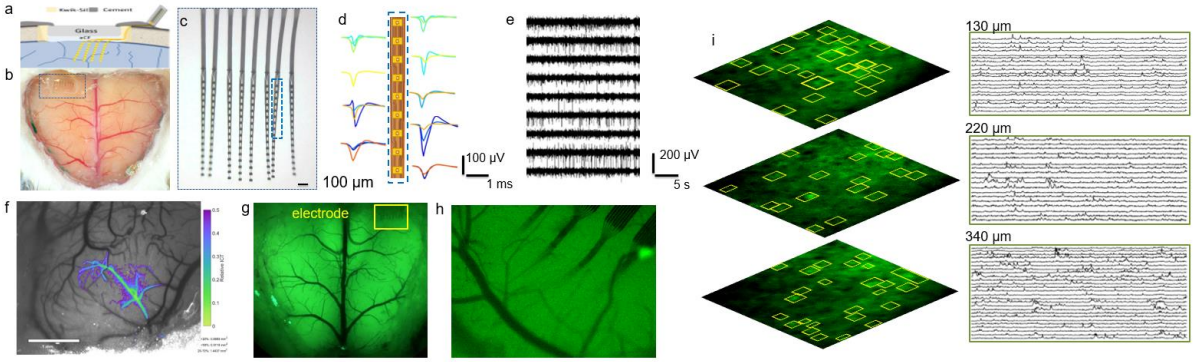


Figure 1. Implanted NET probes in conjunction with cortex-wide optical access. (a) the schematic of implanted electrodes under the cranial window. (b) a nearly-cortex-wide cranial window with an implanted electrode. (c) a representative 128-channel electrodes.1 (d), (e) typical recording performance in the cortex. (f) laser speckle imaging of the hemodynamics near an implanted electrode. (g) epi-fluorescent image of the neocortex of a GCaMP6 mouse. Yellow box indicates the implanted electrodes. (h) enlarged view of the implanted electrodes. (i) two-photon calcium transients of neurons near an implanted electrode (yellow boxes indicate active neurons).

Disclosures: **X. Li:** None. **Z. Zhao:** None. **H. Zhu:** None. **F. He:** None. **L. Luan:** None. **C. Xie:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.05

Topic: I.04. Physiological Methods

Support: R01NS102917
R21NS102964

Title: High density three dimensional ultraflexible electrode array towards stable recording of thousands

Authors: *Z. ZHAO, X. LI, H. ZHU, L. SUN, L. LUAN, C. XIE;
Biomed. Engin., Univ. of Texas at Austin, Austin, TX

Abstract: The brain is a massively-interconnected and constantly-evolving network of specialized circuits, a systematic understanding of which requires an interface that functions at diverse spatial and temporal scales. Implanted electrodes provide a unique approach to decipher brain circuitry by allowing for time-resolved electrical detection of individual neuron activity. However, conventional intracortical recordings are often sparse, and importantly, unstable over long term. Our recent progress on ultraflexible nanoelectronic threads (NETs) [1, 2] has demonstrated marked long-term stable recording and seamless probe-tissue integration. Here we present our on-going efforts of massively expanding this platform towards both high-density volumetric mapping and large-scale distributed recordings in the neocortex and sub-cortical structures with > 1000 recording channels, and doing so with chronic stability. Markedly, we will present volumetric recording densities as high as ~ 1000 channels / μL in the visual cortex of head fixed mice and freely moving rats. We show that > 1000 neurons were simultaneously recorded from ~ 1.3 μL of cortical tissue for over eight weeks. We will further show chronic, large-scale recordings in the hippocamps and in distributed regions across the neocortex. These new capabilities will drive new long-term studies targeting regional and distributed brain circuits. 1. Luan L, Wei X L, Zhao Z T, Siegel J J, Potnis O, Tuppen C A, Lin S Q, Kazmi S, Fowler R A, Holloway S, Dunn A K, Chitwood R A and Xie C 2017 Ultraflexible nanoelectronic probes form reliable, glial scar-free neural integration *Sci. Adv.* **3** 2. Wei X L, Luan L, Zhao Z T, Li X, Zhu H L, Potnis O and Xie C 2018 Nanofabricated Ultraflexible Electrode Arrays for High-Density Intracortical Recording *Adv. Sci.* **5**

Disclosures: **Z. Zhao:** None. **X. Li:** None. **H. Zhu:** None. **L. Sun:** None. **L. Luan:** None. **C. Xie:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.06

Topic: I.04. Physiological Methods

Title: Statistical field theory of nerve impulse generation and propagation

Authors: *G. ZANGARI DEL BALZO;
Theoretical Physics and Complex Systems, European Physical Society and Sapienza Univ., Roma, Italy

Abstract: In this work we suggest a new description at the molecular level of the processes that lead to the generation and propagation of action potentials through the statistical mechanics of disordered systems. In this perspective, the complex behavior of a set of voltage gated ion channels belonging to a nerve cell membrane is described in a closed form by a spin glass. We therefore consider the generation and propagation of action potentials as the necessary and sufficient consequence for a statistical field theory of a set of voltage gated ion channels. This view could allow an in-depth view of the biophysical processes of generation and propagation of action potentials. Some practical applications are also taken into consideration: for example, MRI imaging (fMRI, DW-MRI) could be supplemented by maps of statistical field strengths to detect and monitor the intensity of action potentials in order to build up realistic connectomes and or to help neurosurgery.
Furthermore, it could help the study of demyelinating diseases such as multiple sclerosis and Alzheimer's.

Disclosures: G. Zangari Del Balzo: None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.07

Topic: I.04. Physiological Methods

Support: CONACYT for the Master scholarship 729409

Title: EEG and neurodevelopment in children under one year of age with perinatal risk

Authors: *T. I. HERNÁNDEZ COLOA[1], D. E. GRANADOS RAMOS[2], L. M. PÉREZ FIGUEROA[3], M. M. ÁLVAREZ RAMÍREZ[4];
[1]Maestría en Neuroetología, Inst. de Neuroetología, Univ. Veracruzana, Xalapa-Enríquez, Mexico; [2]Lab. de Psicobiología, Univ. Veracruzana, Xalapa-Enriquez, Mexico; [3]Facultad de Psicología, [4]Facultad de Nutrición, Univ. Veracruzana, Xalapa-Enríquez, Mexico

Abstract: In the first year of life, structural and functional changes of great magnitude are experienced, where is posible adverse factors can affect the acquisition of cognitive and psychomotor skills. Perinatal risk factors are adverse and unfavorable biological and psychosocial indicators that may increase the probability of developmental sequelae that influence neurodevelopment. The objective of this work was to analyze the neurophysiological and neurodevelopmental characteristics in children under one year of age with perinatal risk. A descriptive, exploratory and cross-sectional study was conducted in 10 children from 2 to 9 months with an average age of 5.1 months SD = 2.7 (5 boys, 5 girls). The Neurodevelopment was evaluated with the Infant Development Scale-Bayley II (mental and psychomotor area). The pre, peri and postnatal risk factors were collected by a clinical history, to qualify the risk in three levels: low, medium and high. EEG of 20 channels was made in sleep with the international system 10-20. All children presented risk factors, 6 children had high risk level, 4 with normal development and 2 with delay development; 3 had medium risk, all of them had normal development, 2 psychomotor normal development and 1 psychomotor delay development; 1 with a low level, had mental and psychomotor typical development In the EEG. All children had electrical activity expected for age, however, there were amplitude interindividual differences. In most of the cases with high risk level was observed less amplitude in the EEG and delay development. The follow-up of the development, and neurophysiological characteristics during the first year of life, allows to establish opportune prevention and intervention strategies for the optimal children development.

Disclosures: T.I. Hernández Coloa: None. **D.E. Granados Ramos:** None. **L.M. Pérez Figueroa:** None. **M.M. Álvarez Ramírez:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.08

Topic: I.04. Physiological Methods

Support: JSPS KAKENHI JP19H04993
JSPS KAKENHI JP17H06034
JSPS KAKENHI JP19H04998
JSPS KAKENHI JP17H06039

JSPS KAKENHI JP18KT0021
JSPS CREST JPMJCR16E2
AMED Brain/MINDS JP19dm0207001

Title: Resting state networks on electrocorticograms reveal global and local cortical functional structures

Authors: *M. KOMATSU[1,2], T. YAMADA[3], T. KANEKO[1,4], H. OKANO[4,1], T. YAMAMORI[1], N. ICHINOHE[1,2], Y. YAMASHITA[2];
[1]RIKEN Ctr. for Brain Sci., Saitama, Japan; [2]Natl. Inst. of Neuroscience, Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [3]Grad. Sch. of Computer Sci. and Systems Engin., Kyushu Inst. of Technol., Kyushu, Japan; [4]Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: Resting-state networks (RSNs) in functional magnetic resonance imaging (fMRI), which reflect whole-brain correlations among the blood oxygen level dependent (BOLD) signals in a resting state, have great potentials as a noninvasive method for investigating whole-brain circuitries and as a possible diagnostic tool for disease. In spite of those potentials, their electrophysiological origins have been less studied. To investigate electrophysiological basis of RSNs, we collected resting state electrocorticographic (ECoG) signals, which are comparable to local field potentials (LFPs) on the cortical surface, from three awake common marmosets. The 96ch ECoG array covered almost the entire lateral surface of hemisphere, from the occipital pole to the temporal and frontal poles, and it provides an opportunity to capture global cortical information processing with high resolutions at a sub-millisecond order in time and millimeter order in space. Then, we conducted the independent component analysis (ICA) on the raw ECoG and the band-limited power (BLP) within high-gamma (80-200 Hz) of ECoG, respectively. Here, we assume that the raw ECoG mainly reflect a summation of post-synaptic potentials, while high-gamma BLP is related to a mean firing activity. For each dataset from each subject, we decomposed 96ch ECoG to 30 ICs. Several physiologically meaningful components were selected through visual inspection. RSNs on the raw ECoG included the visual, auditory, sensorimotor, dorsal attention, and frontal networks, and were similar to RSNs on fMRI that previously reported. This result is consistent with the evidence that LFP is correlated with BOLD signals. On the other hand, on the high-gamma BLP, we observed relatively local networks involved in each visual, auditory, sensorimotor, and frontal area. One exception was a network between the frontal pole and areas around temporal sulcus, which is considered as the salience network based on its spatial distribution. The RSNs on ECoG led to an idea that synchronized synaptic communication among distant brain structures forms global networks which are related to RSNs on fMRI, and modulates local networks consisting of spike activity within neighboring areas.

Disclosures: M. Komatsu: None. **T. Yamada:** None. **T. Kaneko:** None. **H. Okano:** None. **T. Yamamori:** None. **N. Ichinohe:** None. **Y. Yamashita:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.09

Topic: I.04. Physiological Methods

Support: DARPA Grant N66001-16-2-4066
EPSRC Grant EP/M506448/1

Title: *In vivo* imaging of neural activity during hippocampal epileptiform discharges with high spatiotemporal resolution using electrical impedance tomography

Authors: *S. HANNAN[1], M. FAULKNER[2], K. ARISTOVICH[1], J. AVERY[3], D. HOLDER[1]; [1]Med. Physics and Biomed. Engin., [2]Wolfson Inst. for Biomed. Res., Univ. Col. London, London, United Kingdom; [3]Dept. of Surgery and Cancer, Imperial Col. London, London, United Kingdom

Abstract: Electrical impedance tomography (EIT) is a functional imaging modality which reconstructs images of internal impedance changes within an object using voltage measurements obtained by applying current through pairs of surface electrodes. EIT has previously been used to image impedance changes that arise due to neural activity during somatosensory evoked potentials and epileptiform discharges through the rat cerebral cortex with a resolution of 2 ms and <300 μm. However, fast neural impedance changes occurring in subcortical regions have never been imaged. Here, we evaluated the feasibility of imaging epileptiform discharges in the rat hippocampus with EIT, using non-penetrating electrodes implanted on the cortical surface. Adult female Sprague-Dawley rats (405-460 g) were anaesthetised with isoflurane. Anaesthesia was maintained with isoflurane and intravenous fentanyl after surgery. A large trapezoidal craniotomy was performed to enable implantation of a 15x9 mm^2 54-electrode array, fabricated from stainless steel and silicone rubber, on the cortical surface of one hemisphere. Epileptiform events were induced in the hippocampus by electrically stimulating the angular bundle of the perforant path with a 2-s train of 1.5 mA biphasic, charge-balanced square-wave pulses at 100 Hz. For EIT recordings, a 100 μA sine wave was applied at 1.4 kHz through an independent epicortical electrode pair for each of ≥30 seizures. Epileptiform discharges were averaged within seizures using trigger markers set at their peak amplitudes, as determined by LFP recordings from the dentate gyrus. After demodulating the impedance signals with a bandwidth of ±500 Hz and reconstructing all processed voltages, EIT images of averaged ictal spikes were generated with a resolution of <300 μm and 2 ms. A maximum impedance change of -0.041 ± 0.013 % was observed in phase with LFP recordings of ictal spikes. EIT images of this impedance decrease could be reproducibly reconstructed with a localisation accuracy of ≤400 μm and revealed a focus of neural activity spatially confined to the dentate gyrus ($p < 0.03125$, $n = 162$ seizures, $N = 5$ rats). This work represents the first experimental evidence of the ability of EIT to image fast electrical activity during neuronal depolarisation in subcortical structures using epicortical electrodes with high spatiotemporal resolution. As such, this technique may be used for improving understanding of functional connectivity between cortical and subcortical regions in

epileptic networks *in vivo*. In addition, EIT holds therapeutic potential for aiding the presurgical localisation of the epileptogenic zone in refractory focal epilepsies.

Disclosures: S. Hannan: None. **M. Faulkner:** None. **K. Aristovich:** None. **J. Avery:** None. **D. Holder:** None.

Nanosymposium

020. High Density Neural Recordings

Location: Room S103

Time: Saturday, October 19, 2019, 1:00 PM - 3:30 PM

Presentation Number: 020.10

Topic: I.04. Physiological Methods

Support: 1 R21 EY 029441 - 01
Whitehall Foundation

Title: CMU array: A fully-customizable, ultra-high density invasive electrode for large-scale recording and optical stimulation enabled through nanoparticle 3D printing

Authors: R. PANAT[1], M. S. SALEH[1], S. RITCHIE[1], M. A. NICHOLAS[2], R. BEZBARUAH[1], *E. A. YTTRI[3];
[1]Mechanical Engin., [2]Biol. Sci., [3]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The needs of electrophysiology have driven neurotechnological advancements - e.g. Neuropixels now provides simultaneous recordings of almost 400 channels (of a possible 960). However, ideal recordings require much more than improved channel count. Sensory, motor and cognitive operations rely upon the coordinated activity of distributed circuits comprising cortical and subcortical structures. Ultimately, research requires targeted, experiment-specific array that can cover a variety of areas throughout the three-dimensional volume of the brain in addition to high channel count and good signal to noise. To this end, we have applied a novel nanoparticle 3D printing method to create the CMU array, a new class of fully-customizable ultra-high-density Massive Microelectrode Array. We demonstrate a CMU array with 512 shanks with multiple shank lengths. The method uses an automated balance of surface and inertia forces of droplets during printing, leading to a rapid construction (hours). The shanks of the array are robust, even with shank diameters as low as 10um. The methods we describe increase the recording sites per unit area by an order of magnitude (>5000 sites/cm^2) and enables an on-demand, study-specific prototyping and manufacture of electrode configurations in a few hours. The CMU array also allows the integration of multiple, independent light delivery fibers for customized photo-identification or stimulation of neurons within the same probe. Furthermore, we have developed a multi-material printing platform to route the high-density electrodes using a multi-layer circuit board on flexible and hard substrates. This advance enables a truly fully-customizable array, free from the constraints of printed circuit boards. The CMU array probes

were successfully inserted into mouse and macaque brains. Low electrochemical impedance of the probes led to a successful recording of action potentials from the brain of anesthetized mice with a high signal to noise ratio. This technology will pave the way to large-scale probes (thousands of channels and/or optic fibers; over several cm^2area) with easily modified probe layouts that can manipulate and capture the dynamics of large, multi-area neural circuits with single-neuron and single-millisecondresolution.

Disclosures: **R. Panat:** None. **M.S. Saleh:** None. **S. Ritchie:** None. **M.A. Nicholas:** None. **R. Bezbaruah:** None. **E.A. Yttri:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.01

Topic: A.02. Postnatal Neurogenesis

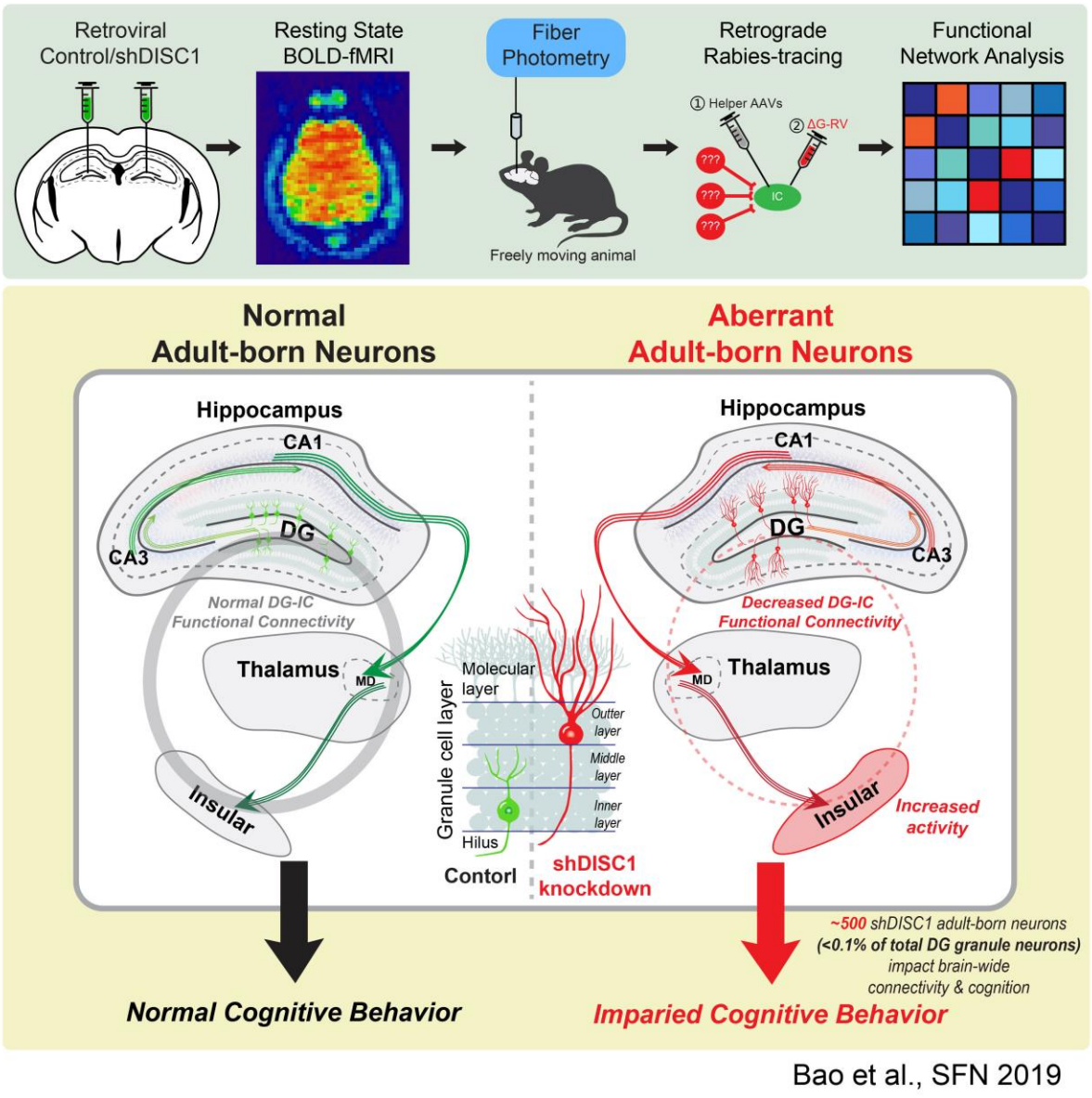
Support: NIH R01MH111773-01
NIH R21AG058160

Title: Dysregulation of hippocampal adult-born neurons disrupts brain-wide functional network

Authors: ***H. BAO**[1], Z. HU[2], S.-H. LEE[1], R. KOLAGANI[1], T.-H. H. CHAO[1], H. SULLIVAN[3], I. R. WICKERSHAM[3], Y.-Y. I. SHIH[1], J. SONG[1];
[1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Univ. of California, Berkeley, CA; [3]McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Mounting evidence suggests that cognitive deficits of several neuropsychiatric disorders, such as schizophrenia and depression, may arise in part from a small number of dysregulated adult-born neurons in the dentate gyrus (DG). Whether dysregulated adult-born neurons contribute to brain-wide maladaptation in neural circuit function and cognitive deficits remains unknown. Our previous study showed that genetic knockdown of Disrupted-in-schizophrenia 1 (DISC1), a genetic risk factor for major mental disorders, exclusively in DG adult-born neurons is sufficient to cause cognitive deficits in behaving mice. Taking advantage of this established mouse model, we performed resting state functional Magnetic Resonance Imaging (rsfMRI) to investigate the brain-wide impact from dysregulated adult-born neurons. Strikingly, we found that approximately 500 DISC1 deficient adult-born neurons (<0.1% of total DG granule neurons) are sufficient to induce a significant decrease of the functional connectivity between DG and insular cortex (IC), two brain regions without direct anatomical connections. Importantly, our in vivo Ca^{2+} imaging confirmed altered IC activity in mice with deficient newborn neurons both at the baseline and during a spatial memory task. Furthermore, our rabies-based retrograde tracing and functional network analysis suggested that dysregulation of

newborn neurons induces an altered DG-IC network intermediated by both local hippocampal and distal thalamic regions. Our results together suggest that modulation of adult-born neurons can potentially impact brain-wide dynamics across several anatomically distinct regions, including those receiving no direct inputs from adult-born neurons. Our findings addressed a long-standing question on how dysregulation of a few hundred adult-born neurons may contribute to the cognitive deficits associated with certain neuropsychiatric conditions.



Bao et al., SFN 2019

Disclosures: H. Bao: None. **Z. Hu:** None. **S. Lee:** None. **R. Kolagani:** None. **T.H. Chao:** None. **H. Sullivan:** None. **I.R. Wickersham:** None. **Y.I. Shih:** None. **J. Song:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.02

Topic: A.02. Postnatal Neurogenesis

Support: NS103981
NS094144

Title: Functions of different autophagy genes in microglia in postnatal neural stem cells

Authors: *X. TANG[1], M. HAAS[2], J.-L. GUAN[2], C. WANG[2];
[1]Univ. of Cincinnati Col. of Med., Cincinnati, OH; [2]Univ. of Cincinnati, COM, Cincinnati, OH

Abstract: Autophagy, the self-degradation process of cytoplasmic content or organelles, has been implicated in physiological conditions and many disease states, including aging, cancers, and neurodegenerative diseases. Our recent studies have indicated that autophagy in postnatal neural stem/progenitor cells (NSCs) regulates the infiltration and activation of residential microglia into the subventricular zone (SVZ) to control neurogenesis. However, the contribution and mechanisms of microglial autophagy to NSCs are not known. In the current study, we conditionally knocked out (cKO) autophagy essential genes of FIP200, Atg14, Atg5, and Atg16, which are involved in different steps of autophagy process, in microglia. We found that conditional knockout of autophagy gene abolished autophagy activity in cultured microglia, but not in cultured astrocytes or in neurons *in vivo*. Deletion of autophagy genes in microglia did not affect their number and morphology in different brain regions, including the neurogenesis niches of SVZ and subgranular zone (SGZ) in dentate gyrus (DG). In both SVZ and SGZ, there was no difference in the number of NSCs ($GFAP^+SOX2^+$), proliferation ($Ki67^+$), and apoptosis ($TUNEL^+$) between cKO mice and corresponding wild type (WT) mice. These results indicated that microglial autophagy had little or no impact on the maintenance of the postnatal NSC pool. Interestingly, we found a significantly decreased percentage of proliferative neuroblasts ($Ki67^+DCX^+$) in both SGZ and SVZ of Atg5 cKO mice, but not in WT mice or other autophagy genes cKO mice. We also injected BrdU for long-term retention to reveal the defective neuronal differentiation ability of NSCs in Atg5 cKO mice. Together, these results suggested an autophagy gene specific mechanism in microglia to regulate postnatal neurogenesis.

Disclosures: X. Tang: None. **M. Haas:** None. **J. Guan:** None. **C. Wang:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.03

Topic: A.02. Postnatal Neurogenesis

Support: NIMH R01, MH070596
NYSTEM Einstein Training Program in Stem Cell Research C30292GG

Title: Enriched environment acts through FGFRs to increase adult hippocampal neurogenesis

Authors: *M. GRONSKA-PESKI, J. M. HEBERT;
Albert Einstein Col. of Med., Bronx, NY

Abstract: The adult hippocampus has a well-established neurogenic niche in mice and many mammals. The neurogenic hippocampal dentate gyrus (DG) generates adult-born neurons capable of integrating into existing circuitry and this process has potential therapeutic value for age-related memory decline and cell replacement. Adult neurogenesis is strongly and positively influenced by enriched environment and exercise (EE/exercise). Yet, molecular pathways that guide the generation, maturation and integration of newly born neurons in response to EE/exercise are poorly understood. Fibroblast Growth Factor Receptors (FGFRs)1-3 are major players in controlling adult-born stem cell maintenance, progenitor cell proliferation, stem cell development and survival. However, what aspects if any of the beneficial effects of EE/exercise are mediated by FGFRs and which intracellular signaling pathways transduce FGFR signals in adult stem/progenitor cells remain unknown. To address the potential fundamental roles of FGFRs on cell proliferation and maintenance on adult neural stem cells we are using FGFR1-3 conditional mutant mice. We found that loss of FGFR1-3 in neurogenic cells generates defects in cell maintenance. Stem/progenitor cells also fail to show an increase 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 (PLCγ) or Fgf Receptor Substrate (FRS) proteins, we demonstrated that in the home cage environment both FGFR1-FRS- and FGFR1-PLC-γ-mediated pathways are non-redundantly required to maintain stem/progenitor cell numbers in the DG, possibly by promoting stem cell expansion. We have also demonstrated that loss of FGFR1-3 in adulthood has an anxiogenic effect. We are currently conducting experiments to understand FGFRs' mechanisms of action on cell maintenance and proliferation in the FGFR1-PLCγ and FGFR1-FRS mutant mice in the EE/exercise environment. 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.

Disclosures: M. Gronska-Peski: None. **J.M. Hebert:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.04

Topic: A.02. Postnatal Neurogenesis

Support: MH109280
MH083317
NS082007
NS090083

Title: Agrin-Lrp4-Ror2 signaling regulates adult hippocampal neurogenesis in mice

Authors: *H. ZHANG[1], A. SATHYAMURTHY[2], F. LIU[2], L. LI[1], L. ZHANG[1], Z. DONG[1], W. CUI[1], X. SUN[2], K. ZHAO[2], H. WANG[1], H.-Y. H. HO[3], W.-C. XIONG[1], L. MEI[1]; [1]Neurosciences, Case Western Reserve Univ., Cleveland, OH; [2]Dept. of Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA; [3]Harvard Med. Sch., Boston, MA

Abstract: Adult neurogenesis in the hippocampus may represent a form of plasticity in brain functions including mood, learning and memory. However, mechanisms underlying neural stem cell (NSC) proliferation are not well understood. We found that agrin, a factor critical for neuromuscular junction formation, is elevated in the hippocampus of mice that are stimulated by enriched environment (EE). Genetic deletion of the *agrin* in excitatory neurons (by NEX-Cre) decreases NSC proliferation and increases depressing-like behavior. Lrp4, a receptor for agrin, is expressed in hippocampal NSC and its mutation (by GFAP-Cre or Nestin-CreER) blocked basal as well as EE-induced NSC proliferation and maturation of newborn neurons. Finally, we show that Lrp4 interacts with and activates Ror2, an orphan receptor tyrosine kinase; and Ror2 mutation (by GFAP-Cre or Nestin-CreER) impair NSC proliferation. Together, these observations identify a role of agrin-Lrp4-Ror2 signaling for adult neurogenesis, uncovering previously unexpected functions of agrin and Lrp4 in the brain.

Disclosures: H. Zhang: None. **A. Sathyamurthy:** None. **F. Liu:** None. **L. Li:** None. **L. Zhang:** None. **Z. Dong:** None. **W. Cui:** None. **X. Sun:** None. **K. Zhao:** None. **H. Wang:** None. **H.H. Ho:** None. **W. Xiong:** None. **L. Mei:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.05

Topic: A.02. Postnatal Neurogenesis

Support: ANR- 13-BSV4-0013
FRM ING20150532361
FRM FDT20160435597

Title: Neuronal integration in the adult olfactroy bulb is a non selective addition process

Authors: *J.-C. J. PLATEL[1], A. ANGELOVA[1], S. BUGEON[2], J. WALLACE[3], T. GANAY[1], I. CHUDOTVOROVA[1], J.-C. DELOULME[5], C. BÉCLIN[1], M.-C. TIVERON[1], N. CORÉ[1], V. N. MURTHY[4], H. CREMER[1];
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Abstract: Adult neurogenesis is considered a competition in which neurons scramble during a critical period for integration and survival. Moreover, newborn neurons are thought to replace preexisting ones that die. Despite indirect evidence supporting this model, systematic *in vivo* observations are still scarce. We used 2-photon *in vivo* imaging combined with low dose thymidine analog pulse chase experiments to study neuronal integration and survival in the olfactory bulb (OB). We show that cell-loss in the OB occurs only at low levels. Neuronal death resembling a critical period was induced by standard doses of thymidine analogs, but disappeared when low doses of EdU were used. Finally, we demonstrate that the OB grows throughout life. This shows that neuronal selection during OB-neurogenesis does not occur during integration and argues against the existence of a critical period for survival. Moreover, the OB is not a turnover system but shows lifelong neuronal addition.

Disclosures: **J.J. Platel:** None. **A. Angelova:** None. **S. Bugeon:** None. **J. Wallace:** None. **T. Ganay:** None. **I. Chudotvorova:** None. **J. Deloulme:** None. **C. Béclin:** None. **M. Tiveron:** None. **N. Coré:** None. **V.N. Murthy:** None. **H. Cremer:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.06

Topic: A.02. Postnatal Neurogenesis

Support: Spanish Ministry of Economy and Competitiveness (SAF-2017-82185-R and RYC-2015-171899) (María Llorens-Martín)
The Alzheimer´s Association (2015-NIRG-340709 and AARG-17-528125 (María Llorens-Martín))
The Association for Frontotemporal Degeneration (2016 Basic Science Pilot Grant Award (María Llorens-Martín))
Comunidad de Madrid (PEJD-2017-PRE/BMD-3439 (María Llorens-Martín))
Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED, Spain) (Jesús Ávila)

Title: Adult hippocampal neurogenesis during physiological and pathological aging in humans

Authors: E. P. MORENO-JIMÉNEZ[1], M. FLOR-GARCÍA[1], J. TERREROS-RONCAL[1], A. RABANO[2], F. CAFINI[3], N. PALLAS-BAZARRA[4], J. AVILA[5], ***M. LLORENS-MARTIN**[1];
[1]Mol. Biol., Univ. Autonoma De Madrid, Madrid, Spain; [2]Fundacion CIEN, Madrid, Spain; [3]Univ. Europea de Madrid, Madrid, Spain; [4]Ctr. De Biologia Mol. Severo Ochoa (CBMSO), Madrid, Spain; [5]CIBERNED, Madrid, Spain

Abstract: Memory impairment in several neurodegenerative diseases can be attributed to a significant decline in the functioning of the hippocampal formation, a brain region crucial for learning and memory. Moreover, this structure hosts one of the most unique phenomena of the adult mammalian brain, namely the addition of new neurons throughout lifetime. While synapse loss and consequent death of mature neurons may be responsible for much of the hippocampal malfunctioning in these diseases, studies in mice suggest that neurodegenerative diseases could also target the generation of new neurons - or adult hippocampal neurogenesis (AHN). In this study, we revisited the occurrence of continued neurogenesis in the human hippocampus of healthy subjects and patients with distinct neurodegenerative diseases, using brain material obtained under tightly controlled conditions and applying state-of-the-art tissue processing methods. Our data evidence that AHN is a robust phenomenon in the human brain, and points to impaired neurogenesis as a potentially relevant mechanism underlying neurodegenerative processes that may be amenable to novel therapeutic strategies.

Disclosures: M. Llorens-Martin: None. **E.P. Moreno-Jiménez:** None. **M. Flor-García:** None. **J. Terreros-Roncal:** None. **A. Rabano:** None. **J. Avila:** None. **N. Pallas-Bazarra:** None. **F. Cafini:** None.

Nanosymposium

102. Molecular Mechanisms of Adult Neurogenesis

Location: Room S404

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 102.07

Topic: A.02. Postnatal Neurogenesis

Title: Modulation of hippocampal neurogenesis in awake rats by electrical & chemical thalamic stimulation

Authors: *F. CHAMAA[1], B. DARWISH[4], E. D. AL-CHAER[2], Z. NAHAS[5], N. E. SAADE[6], W. ABOU-KHEIR[3];
[1]Anatomy, Cell Biol. and Physiological Sci., [2]Dept. of Anatomy, Cell Biol. & Physiological Sci., [3]American Univ. of Beirut, Beirut, Lebanon; [4]Anatomy, Cell Biol. and Physiological Sci., American Univ. Of Beirut, Beirut, Lebanon; [5]Univ. of Minnesota, Minneapolis, MN; [6]American Univ. of Beirut, Beirut, Lebanon

Abstract: Deep brain stimulation (DBS) provides clinical benefit for a variety of neurological disorders, but the underlying mechanism of how it alters neural activity remains ill-understood. Our group showed that DBS to the anteromedial thalamic nucleus (AMN) in awake rats modulates adult hippocampal neurogenesis. As DBS might induce off-targets effects, we sought to specifically stimulate the cell bodies of AMN by chemical stimulation using low doses of Kainic acid (KA). This study included two groups of adult male sprague-dawley rats: Group 1 received 6-sessions of unilateral DBS in the right AMN & group 2 received implants of mini-osmotic pumps in same region releasing KA (500pM) at a rate of 1μl/injection/hr/7days. Sham animals were included for both groups. All rats received BrdU injections during stimulation & were followed for 4 weeks. Novel arm exploration was examined using the Y-maze, & co-labeling of BrdU/NeuN cells was counted in the dentate gyrus. Four weeks after DBS, BrdU+/NeuN+ mature neurons were 3-folds higher than sham. Continuous micro-perfusion of KA increased the number of mature neurons to 4-folds higher than vehicle. The Y-maze test showed that both electrical and chemical stimulation to the AMN enhanced novel arm exploration at 4-weeks after stimulation. The current study presents hippocampal neurogenic responses to electrical & chemical stimulation & reveals a translational behavioral enhancement of hippocampal-related skills following stimulation. It highlights the importance of glutamic kainate receptor activation in the AMN nucleus in modulating hippocampal neurogenesis.

Disclosures: F. Chamaa: None. **B. Darwish:** None. **E.D. Al-Chaer:** None. **Z. Nahas:** None. **N.E. Saade:** None. **W. Abou-Kheir:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.01

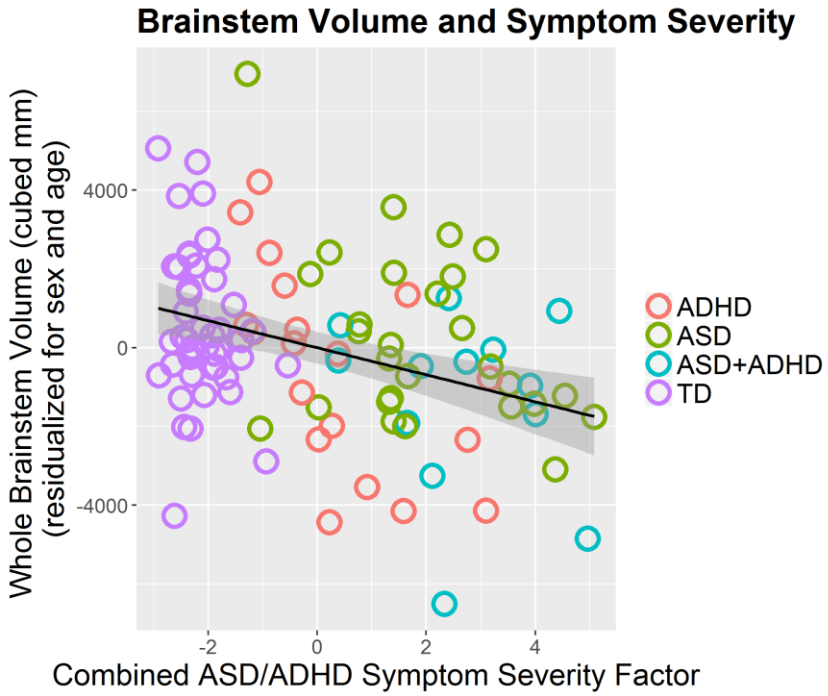
Topic: A.07. Developmental Disorders

Support: Hartwell Foundation Individual Biomedical Award
Austin Faculty Fellowship
NIH Grant P30 HD003352
NIH Grant U54 HD090256
NIH Grant R01 HD094715

Title: Brainstem correlates of combined autism spectrum and attention-deficit/hyperactivity symptoms in children

Authors: *B. TRAVERS[1], J. LI[1], O. J. SURGENT[1], O. DADALKO[2], A. L. ALEXANDER[1], S. KECSKEMETI[1], D. DEAN, III[1];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Waisman Ctr., Madison, WI

Abstract: Autism spectrum disorder (ASD) frequently co-occurs with attention-deficit/hyperactivity disorder (ADHD), and individuals with ASD are 22 times at higher risk of having ADHD compared with those without ASD. Yet, it is unclear what the brain basis of this biological overlap may be. Given the brainstem's role in attention and sensory gating, the objective of the present study was to investigate the structural properties of the brainstem in light of co-occurring ASD and ADHD symptoms. In the present study, 105 children (6-10 year olds) completed motion-corrected T1-weighted MPnRAGE scans and ASD and ADHD symptom severity measures. Of the 105 children, 41 had ASD (1/3 with a co-diagnosis of ADHD), 19 had ADHD without ASD, and 45 children had typical development. Approximately 1/3 of the sample were female. A latent variable for ASD/ADHD symptom severity was created from multiple measures of the core ASD social, communication, sensory, and repetitive behavior symptoms and measures of ADHD inattention and hyperactivity. All symptom measures showed robust factor loadings onto a single latent factor, which accounted for 74% of the variance in combined ASD/ADHD symptom severity. Freesurfer 6.0.0 was used to segment the whole brainstem and then further segment the brainstem into the midbrain, pons, superior cerebellar peduncle, and medulla. The results showed that across the participants, smaller brainstem volume was associated with more severe ASD/ADHD symptoms. This association remained after accounting for age, sex, and intracranial volume. This association further remained after excluding the children with typical development. Follow-up analyses suggested that the strongest correlations with ASD/ADHD symptom severity were within the pons and medulla of the brainstem. This work suggests that the brainstem may be intimately related to the overlapping symptoms observed in children with ASD and ADHD. Future research will examine structural properties within the brainstem to better understand what brainstem properties might be driving these volumetric effects.



Disclosures: **B. Travers:** None. **J. Li:** None. **O.J. Surgent:** None. **O. Dadalko:** None. **A.L. Alexander:** None. **S. Kecskemeti:** None. **D. Dean:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.02

Topic: A.07. Developmental Disorders

Support: CONACYT for the PhD scholarship no. 931776

Title: Electroencephalographic signal characterization using an emotion recognition test in ASD children

Authors: *B. SANABRIA[1], D. E. GRANADOS[2];
[1]Doctorado en Ciencias Biomédicas, Ctr. de Investigaciones Biomédicas-Laboratorio de Psicobiología, Univ. Veracruzana, Xalapa-Enríquez, Mexico; [2]Lab. de Psicobiología, Univ. Veracruzana, Xalapa-Enriquez, Mexico

Abstract: This study is a part of a PhD project called an algorithm to discriminate between a normal and ASD electroencephalogram, in order to have a support tool for an early diagnosis of the disorder. Opportune diagnosis allows the children with ASD receive timely therapies that will help them to integrate in better way in the society, because it is known that children who receive treatments in early age achieve better results. The aim of this study was characterize an electroencephalographic signal using the N170 and an emotion recognition test in ASD children. A test protocol related with the emotion recognition was created to evaluate the N170, and it was evaluated and approved by an ethics committee. The test consisted in show 360 visual stimuli, of which 300 corresponded to images of faces with the four basic emotions: joy, sadness, anger and fear (Jack,2016), and a neutral expression. The other 60 stimuli were images of three different objects: a ball, a butterfly and an airplane. All these images were showed for 850 ms and between them an image of a fixation cross was placed with a variable duration of 500 to 1600 ms. The test lasted 14 min approximately. The objects were showed to keep the attention of the children in the test. Otherwise, the fixation cross was used to avoid that the brain habituates to the visual stimuli. The test was presented to five children with ASD and five with typically developing between 6 and 10 years old (age average=10). This was showed to the children individually into a silence room while an electroencephalographic register of 19 electrodes was taken to obtain the N170. The instruction to the children before they started the test was: “In the computer screen you will see different faces and objects, when you see a ball, a butterfly or an airplane, you need to press the red button”. The results evidence that the latency was similar in both groups of the study, nevertheless the magnitude of the amplitude was lower in children with

ASD. These results will be implemented into the algorithm, and then, it can be used in ASD children in order to give them therapies at earlier.

Disclosures: B. Sanabria: None. **D.E. Granados:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.03

Topic: A.07. Developmental Disorders

Title: Determining behavioral phenotypes under genetic influence in autism spectrum disorder

Authors: *N. T. STOCKHAM[1], K. PASKOV[2], D. P. WALL[3];
[1]Neurosciences, [2]Biomed. Informatics, [3]Pediatrics, Biomed. Data Sci., Stanford Univ., Stanford, CA

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopment disorder with consistently high heritability estimates. However, the genetic architecture of inherited ASD risk remains elusive despite several studies of tens of thousands of individuals. A possible explanation for this lack of discovery is that ASD encompasses several disorders with distinctly different genetic etiologies. Determining which aspects of the ASD phenotype are most reflective of genetic influence could recover statistical power. For this purpose we developed a novel statistical approach and computational method to parse item-level ASD behavioral instrument data to determine which aspects of the autism phenotype are consistent with genetic influence. For this work we created a Structured Causal Model (SCM) for ASD given current knowledge. Using this SCM, we derived a criterion to determine if a given phenotype scoring algorithm reflects genetic influence. We also created a computational method using convex optimization to construct novel phenotype scoring algorithms. We applied these new methods to the Autism Diagnostic Interview Revised (ADIR) behavioral instrument data in the AGRE dataset, consisting of 1272 families with multiple children with ASD. We found that the ADIR "Reciprocal Social Interaction" (RSI) score is a consistent measure of genetic influence, whereas the ADIR "Restricted, Repetitive, and Stereotyped Patterns" (RRSP) score is not a consistent measure of genetic influence. The ADIR "Communication" (C) score is a consistent measure of both genetic and non-genetic influences. The computational method created several novel phenotype scoring algorithms consistent with genetic influence directly from the item-level ADIR phenotype data. These novel scoring algorithms highlighted ~5% of multiplex families in the AGRE collection that are inconsistent with sharing a genetic cause of ASD. The inference that the ADIR RSI score reflects genetic influence, while the ADIR RRSP score does not, is strikingly consistent with recent vasopressin biomarker studies by Karen Parker (Parker 2018) that show high correlation of CSF vasopressin levels with the ADIR RSI score, but no

correlation with the RRSP score. This work advances ASD research by rigorously examining current phenotypic measures of ASD while also introducing a novel computation method to construct new phenotype scoring algorithms for ASD from both established behavioral questions and novel video data.

Disclosures: **N.T. Stockham:** None. **K. Paskov:** None. **D.P. Wall:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.04

Topic: A.07. Developmental Disorders

Support: the Chinese Academy of Sciences Strategic Priority Research Program B grants XDBS1020100
the Beijing Municipal Science & Technology Commission Z181100001518001

Title: Modeling autism using non-human primates

Authors: *Y. Q. ZHANG[1], **H. ZHAO**[2,1], Z. TU[3], B. LI[4], Y.-H. JIANG[5], X. LI[6];
[1]Inst. of Genet. and Developmental Biology, Chinese Acad. of Sci., Beijing, China; [2]Guangzhou Inst. of Biomedicine and Health, Chinese Acad. of Sci., Guangzhou City, China; [3]Ministry of Educ. CNS Regeneration Collaborative Joint Lab., Guangdong-Hongkong-Macau Inst. of CNS Regeneration, Jinan Univ., Guangzhou, China; [4]Guangdong-Hongkong-Macau Inst. of CNS Regeneration, Jinan Univ., Guangdong, China; [5]Dept. of Pediatrics and Neurobio., Duke Univ. Sch. of Med., Durham, NC; [6]Human Genet., Emory Univ., Atlanta, GA

Abstract: Mutations in *SHANK3* and *CHD8* remain a few top replicated genetic defects in autism spectrum disorders (ASD) in humans. Although a number of mouse models with *Shank3* or *CHD8* mutations have been valuable for investigating the pathogenesis of ASD, species-dependent differences in brain structures and behaviors post considerable challenges to use rodents to model ASD and to translate experimental results to the clinic. We have used CRISPR/Cas9 to generate cynomolgus monkey models by disrupting both *SHANK3* and *CHD8*. Systematic analyses including biochemical, histological, proteomic, and RNA-sequence revealed apparent brain developmental defects in *SHANK3* and *CHD8* mutants, offering previously unappreciated neuropathology defects associated with autism (Zhao et al., Cell Research, 2017). Behavioral analysis of the live *SHANK3* and *CHD8* mutant monkeys revealed core abnormalities of ASD, including impaired social interaction and repetitive behaviors in *SHANK3* mutants. Importantly, these abnormal behaviors in *SHANK3* mutant were alleviated by the antidepressant fluoxetine treatment (Tu et al., Human Molecular Genetics, 2019). Our findings provide the first

demonstration that the genetically modified non-human primate can be effectively used for translational research of therapeutics for ASD.

Disclosures: **Y.Q. Zhang:** None. **H. Zhao:** None. **Z. Tu:** None. **B. Li:** None. **Y. Jiang:** None. **X. Li:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.05

Topic: A.07. Developmental Disorders

Support: SFARI award # 367560
NIH Grant T32GM007616

Title: Autism associated missense variants impact locomotion and neurodevelopment in *Caenorhabditis elegans*

Authors: ***W.-R. S. WONG**[1], K. I. BRUGMAN[1], S. MAHER[1], J. OH[1], K. HOWE[2], P. W. STERNBERG[1];
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Abstract: Missense mutations account for a large proportion of genetic variants in human diseases, including autism spectrum disorder (ASD). The causal relationship of most missense variants in the pathogenesis of ASD has not yet been demonstrated, and an experimental method systematically prioritizing missense alleles can gain crucial insight into the molecular basis for disease pathology. We thus designed a pipeline that uses *C. elegans* as a genetic model to screen for phenotype-changing missense alleles inferred from human ASD studies. We identified highly conserved human ASD-associated missense variants in their *C. elegans* orthologs, used a CRISPR/Cas9-mediated homology-directed knock-in strategy to generate missense mutants, and analyzed their impacts on behaviors and development via several broad-spectrum assays. We found that 19% of the human disease-associated alleles have conserved position in their *C. elegans* orthologs. Among the genes we tested, 70% of the missense variants predicted to perturb protein function showed detectable phenotypic changes in morphology, locomotion, or fecundity. Our findings indicate that certain missense variants in the *C. elegans* orthologs of ASD candidate genes *ALDH1A3*, *AMPD1*, *BCL11A*, *BRAF*, *CACNA1D*, *CHD7*, *CHD8*, *CUL3*, *DLG4*, *ELAVL3*, *GLRA2*, *KDM6B*, *NAA15*, *PTEN*, *SPARCL1*, *SYNGAP1*, *TPH2*, and *TRIO* impact neurodevelopment and locomotion functions. We also made ASD-associated missense mutants in *ADSL*, *ATP2B2*, *EFR3A*, *EP400*, *GNAS*, *KMT2C*, *MAPK3*, *NLGN4X*, *NRXN1*, *P4HA2*, *PAX6*, *SHANK3*, *SLC6A1*, and *TBR1*. Further phenotypic characterization of *BRAF* and

other genes are continuing. Our approach will help assess the impact of a single missense mutation in the whole organism and prioritize consequential missense variants for further intensive analysis in vertebrate models and human cells.
Keywords: missense variants, CRISPR knock-in, locomotion, fecundity, autism spectrum disorder (ASD), phenotype prediction, disease modeling

Disclosures: W.S. Wong: None. **K.I. Brugman:** None. **S. Maher:** None. **J. Oh:** None. **K. Howe:** None. **P.W. Sternberg:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.06

Topic: A.07. Developmental Disorders

Support: Tufts University Inflammation Based Seed Grant

Title: Traffic related particulate matter affects behavior, inflammation, and neuronal integrity in a developmental rodent model

Authors: *B. NEPHEW[1], A. NEMETH[2], N. HUDDA[3], J. PETTITO[1], G. POIRIER[4], W. ZAMORE[3], G. BEAMER[5], J. A. KING[1], J. DURANT[3], D. BRUGGE[6];
[1]Worcester Polytechnic Inst., Worcester, MA; [2]Tufts Univ., North Grafton, MA; [3]Tufts Univ., Medford, MA; [4]Psychiatry, Ctr. for Comparative NeuroImaging, Umass Med. Sch., Worcester, MA; [5]Tufts Univ. Cummings Sch., North Grafton, MA; [6]Univ. of Connecticut, Storrs, CT

Abstract: BACKGROUND: Substantial epidemiological and experimental evidence indicates that fine airborne particulate matter (PM), particularly of traffic-related origin, can damage both the cardiovascular and respiratory systems. Recent evidence has implicated fine particles in the etiology of cognitive delay, depression, anxiety, autism, and neurodegenerative diseases. **OBJECTIVES:** We assessed the effects of gestational and early life exposure to environmentally-relevant levels of PM on the social and anxiety related behaviors, cognition, inflammatory markers, and neuronal integrity in male rat juveniles. **METHODS:** Gestating and lactating rats were exposed to traffic related PM for 5 hours/day, 5 days/week for 6 weeks (3 weeks gestation, 3 weeks lactation); target exposure concentrations for nebulized fine PM fraction were 200 $\mu g/m^3$. To assess anxiety and cognitive function, F1, male juveniles underwent elevated platform, cricket predation, nest building, social behavior and marble burying tests at 32-60 days of age. Several cytokines and growth factors were measured in F1 male juveniles upon completion of behavioral testing, and brains were analyzed with diffusion tensor MRI to assess neuronal integrity. **RESULTS:** PM exposure had no effect on litter size or weight, or offspring growth. F1 litters developmentally exposed to PM exhibited significantly increased

anxiety (p =0.04), decreased cognition reflected in poorer nest-organization (p =0.04), and decreased social play and allogrooming (p= 0.003). MRI analysis of ex vivo brains revealed decreased structural integrity of neuronal tissues in the anterior cingulate and hippocampus in F1 juveniles exposed to PM ($p<0.01$, $p=0.03$, respectively). F1 juvenile males exposed to PM exhibited significantly decreased plasma levels of both IL-18 ($p=0.03$) and VEGF ($p=0.04$), and these changes were inversely correlated with anxiety related behavior. **CONCLUSIONS:** Chronic exposure of rat dams and their offspring to environmentally relevant levels of traffic-related PM during gestation and lactation decreases social behavior, increases anxiety, impairs cognition, decreases basal levels of IL-18 and VEGF (which are correlated with behavioral changes), and disrupts neuronal integrity in the juvenile male offspring.

Disclosures: B. Nephew: None. **A. Nemeth:** None. **N. Hudda:** None. **J. Pettito:** None. **G. Poirier:** None. **W. Zamore:** None. **G. Beamer:** None. **J.A. King:** None. **J. Durant:** None. **D. Brugge:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.07

Topic: A.07. Developmental Disorders

Support: R01 NIH HD092593
R01 NIH HD092593-01
SFARI (Simons Foundation Autism Research Initiative) Pilot Award

Title: Preterm ASD risk linked to cerebellar white matter changes

Authors: *C.-M. VACHER, S. SEBAOUI, H. LACAILLE, J. SALZBANK, J. O'REILLY, D. BAKALAR, P. KRATIMENOS, A. PENN;
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Abstract: The placenta is an essential contributor to fetal brain development. It not only mediates maternal-fetal exchanges, but also produces hormones able to reach the fetal brain and potentially support its development. Compromised function or premature loss of placenta has been linked to diverse neurodevelopmental disorders. Allopregnanolone (ALLO), a progesterone derivative neurosteroid made by the placenta, is a potent positive modulator of the GABAA receptor, the principal mediator of the fast inhibitory transmission within the brain. To address the contribution of placental ALLO on brain development and long-term behavior, we have generated a novel mouse model in which the gene encoding the synthesis enzyme for ALLO (*Akr1c14*) is specifically deleted in trophoblasts using a tissue-specific Cre-Lox strategy. Here we show that placental ALLO insufficiency is associated with sex-specific white matter (WM)

abnormalities in the cerebellum. Behavioral testing revealed increased repetitive behavior and sociability deficit, two hallmarks of autism spectrum disorder (ASD), in the male offspring only, but no severe motor impairment. Furthermore we found a positive correlation between the cerebellar contents of myelin basic protein (MBP) and the severity of ASD-like behaviors. A single injection of ALLO during gestation was sufficient to completely rescue both cerebellar MBP levels and behavior in plKO littermates. By providing new evidence on the importance of placental hormones on shaping and programing the developing brain, our data paves the way for further investigation in the field of neuroplacentology, and allows us considering novel therapeutic approaches to prevent the neurological outcomes of preterm birth or placental dysfunction.

Disclosures: C. Vacher: None. **S. Sebaoui:** None. **H. Lacaille:** None. **J. Salzbank:** None. **J. O'Reilly:** None. **D. Bakalar:** None. **P. Kratimenos:** None. **A. Penn:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.08

Topic: A.07. Developmental Disorders

Support: NIH 5R21MH116681-02

Title: Maternal immune activation perturbs transcriptional co-expression networks during corticogenesis

Authors: *K. CICHEWICZ[1], C. P. CANALES[1], M. ESTES[1], I. ZDILAR[1], L. SU-FEHER[1], T. PHAM[1], J. GOON[1], K. E. PRENDERGAST[1], K. M. FARRELLY[1], L. HAAPANEN[2], J. VAN DE WATER[2], A. K. MCALLISTER[1], A. S. NORD[1];
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Abstract: Maternal infection is the one of the most compelling environmental risk factors for neurodevelopmental disorders, including autism and schizophrenia. Understanding the molecular pathways dysregulated by maternal immune activation (MIA) is critical for understanding the pathophysiology of these disorders. Here, we identified gene expression changes in the fetal mouse cortex following mid-gestation MIA at embryonic day 12.5 (E12.5) via intraperitoneal injection of the viral mimic polycytidylic acid poly(I:C). We performed RNA-Seq on cortical samples dissected at E12.5+6h, E14.5, E17.5, and postnatal day 0 (P0), and modeled systems-level impacts on gene co-expression networks via Weighted Gene Network Correlation Analysis (WGCNA). We identified a strong transient acute E12.5+6h signature, including response to stress, defense response to virus, and angiogenesis. The acute phase is followed by alterations in proliferation, neuronal differentiation, astrogenesis, synaptogenesis, and cortical lamination that

emerge at E14.5 and peak at E17.5. Our temporal modeling approach revealed that MIA accelerates the transcriptional developmental program at E17.5, which largely resolves by birth. Though we did not observe gross neuroanatomical pathologies, our findings suggest that the cellular composition of the cortex is altered in MIA offspring, which may be evident by persistent activation of some of the immune pathways at P0. WGCNA identified six gene co-expression modules corresponding to major neurodevelopmental processes and immune/stress pathways. Those modules and their relevant processes were differentially affected by MIA. Interleukin 6 (IL-6) has been reported as a key mediator of the poly(I:C) MIA immune response. By co-administering an IL-6 inhibitor together with poly(I:C) at E12.5, we were able to partially rescue the MIA transcriptional signature assayed at E14.5 and P0, indicating the potential therapeutic relevance of this approach. Genes that are rescued most efficiently by the inhibitor mediate immune signaling. In summary, our transcriptomic analysis provides detailed insight into the neurodevelopmental processes affected by poly(I:C) MIA in the fetal brain throughout gestation, and reveals the molecular pathways downstream of IL-6 activation in this model. Our results are also important in considering the efficacy of potential therapeutic approaches using IL-6 inhibitors.

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Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.09

Topic: A.07. Developmental Disorders

Support: NIH R01GM103842

Title: Inefficient thermogenic mitochondrial respiration due to futile proton leak in a mouse model of fragile x syndrome

Authors: ***R. J. LEVY**[1], K. GRIFFITHS[3], A. WANG[3], L. SUN[4], G. YANG[2], P. LICZNERSKI[5], E. A. JONAS[6];
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Abstract: Introduction: Fragile X syndrome (FXS) is the leading known inherited intellectual disability and most common genetic cause of autism. FXS manifests from silencing of *Fmr1*

gene expression. Mitochondrial dysfunction underlies cognitive impairment and behavioral abnormalities in other syndromes and has been linked to autism, however, has not been adequately evaluated in FXS. Thus, we aimed to identify discrete defects within mitochondria and establish a causative link with the FXS phenotype. We hypothesized that mitochondria would be dysfunctional in the developing FXS forebrain. Methods: We evaluated male *Fmr1* KO mice and controls on P10 and measured forebrain mitochondrial O_2 consumption, membrane potential, ETC complex activities, coenzyme Q (CoQ) levels, and calcium loading capacity. Intravital microscopy and calcein-cobalt assays were performed. Phenotypic FXS features were assessed 24 hours after ip CoQ injection on P9 and 8 weeks later. We evaluated 6-12 mice per group. Significance was assessed via t-test and ANOVA testing. Results: *Fmr1* KOs demonstrated elevated temperature and lactate, suggesting anaerobic glycolysis and uncoupled thermogenic respiration. State 3 respiration was decreased in *Fmr1* KOs, however, O_2 consumption was coupled and ETC complex activities were relatively normal. Complex I+III and II+III activities were impaired and CoQ levels were significantly decreased in *Fmr1* KOs. Rescue of forebrain II+III activity was achieved *in vitro* with a CoQ analogue and *in vivo* following ip CoQ_{10} injection in *Fmr1* KOs, confirming a CoQ defect. Modular kinetics elicited a voltage-gated pathological proton leak in *Fmr1* KO mitochondria that was blocked with cyclosporine A and CoQ_1 , suggesting opening of the mitochondrial permeability transition pore (mPTP). Defects in *Fmr1* KO forebrain calcium loading capacity were sensitive to CSA and CoQ_1 and intramitochondrial calcein quenching confirmed pathological opening of the mPTP. Repletion of mitochondrial CoQ within the *Fmr1* KO forebrain closed the channel, blocked pathological proton leak, restored rates of protein synthesis during synaptogenesis, and normalized key phenotypic features later in life.
Conclusions: CoQ deficiency caused a pathologically open mPTP in developing FXS brain mitochondria. The open mPTP resulted in futile proton conductance and is the source of uncoupled thermogenic respiration in *Fmr1* KOs. Importantly, CoQ restored defects in electron transport and closed the pathologic leak. We further found that *in vivo* CoQ administration rescued hallmark phenotypic features in *Fmr1* KOs mice, establishing a causative link.

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Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.10

Topic: A.07. Developmental Disorders

Support: FRAXA Research Foundation
NIH Grant UL1TR002373

Title: The ketogenic diet rescues Fmr1^{KO} phenotypes

Authors: *P. R. WESTMARK, A. GUTIERREZ, A. GHOLSTON, T. WILMER, R. K. MAGANTI, **C. J. WESTMARK**;
Neurol., Univ. Wisconsin, Madison, WI

Abstract: In addition to intractable epilepsy, the ketogenic diet (KD) is showing beneficial effects in cancer, obesity, diabetes and neurodegeneration. We sought to determine if the KD attenuated disease phenotypes in *Fmr1^{KO}* mice. Juvenile mice were weaned onto KD versus control diet at postnatal day 18 and tested for seizure susceptibility in the audiogenic-induced seizure (AGS) assay and for alterations in circadian hyperactivity by actigraphy. We typically observe 50-90% reduction in wild running, which precedes seizures in the AGS assay, and 100% rescue of seizure and death outcomes in response to acute treatment with mGluR$_5$ inhibitors in *Fmr1^{KO}* mice. In response to the KD, we observed 3% wild running, seizures and deaths in response to 110 dB audiogenic stimulation in male mice. In contrast, the KD did not attenuate seizure phenotypes in female *Fmr1^{KO}* mice indicating a strong sex-specific difference in response to KD. We have tested several thousand mice in the AGS assay over the past decade in response to over two dozen pharmaceutical, dietary or genetic interventions. The attenuation in male mice in response to KD is comparable to or better than the best mGluR$_5$ inhibitors we have tested. This is the first time we have observed a strong sex-specific response to an intervention. In addition to juvenile seizures, the KD affects diurnal rest-activity rhythms in adult *Fmr1^{KO}* mice and WT littermates. Actigraphy is a sensitive, noninvasive, reliable biomarker to measure rest-activity cycles. There are contradictory reports regarding hyperactivity in *Fmr1^{KO}* mice. We binned our data into 6-hr quadrants (first and second half of the light cycle and first and second half of the dark cycle) and observe a highly reproducible, statistically significant 40% increase in activity in *Fmr1^{KO}* mice during the 6am-noon quadrant, which is the first half of the light cycle. If we analyze in 12-hr bins, the difference is masked. Mice are nocturnal; thus, this period corresponds to the animals having trouble “falling asleep” and correlates with sleep problems in FXS children. In response to the KD, we replicated this finding (P=0.04), and activity was significantly decreased in *Fmr1^{KO}* mice in response to the KD in 3 of 4 binned timeframes (12am-6am, 6am-noon and 6pm-midnight).

Disclosures: P.R. Westmark: None. **A. Gutierrez:** None. **A. Gholston:** None. **T. Wilmer:** None. **R.K. Maganti:** None. **C.J. Westmark:** None.

Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.11

Topic: A.07. Developmental Disorders

Support: FRAXA Fellowship
NIH Grant MH092877

Title: Activation of autophagy rescues cognitive and sensory deficits in fragile X mice

Authors: *J. YAN[1], M. W. PORCH[1], B. COURT-VAZQUEZ[1], M. V. BENNETT[2], R. ZUKIN[3]; [2]Dominick P Purpura Dept. of Neurosci., [1]Albert Einstein Col. of Med., Bronx, NY; [3]Dept Neurosci, Albert Einstein Col. Med., Bronx, NY

Abstract: Fragile X syndrome (FXS) is the most common form of heritable intellectual disabilities and a leading genetic cause of autism. Fragile X (*Fmr1* KO) mice exhibit aberrant dendritic spine structure and synaptic plasticity, sensory hypersensitivity, cognitive and social deficits. Autophagy is a catabolic process of programmed degradation and recycling of proteins and cellular components via the lysosomal pathway. However, a role for autophagy in the pathophysiology of Fragile X syndrome is, as yet, unclear. Here we show that autophagic flux, a functional readout of autophagy, and biochemical markers of autophagy are impaired in hippocampal neurons of Fragile X mice (Yan et al, 2018). Activation of autophagy by delivery of shRNA to Raptor directly into the CA1 of living mice corrects aberrant spine structure, synaptic plasticity and cognition in hippocampal neurons of Fragile X mice. Activation of autophagy also corrects overabundant PSD-95 and Arc, synaptic proteins implicated in spine structure and synaptic plasticity, identifying a potential mechanism by which impaired autophagy in hippocampus is causally related to the Fragile X phenotype (Yan et al, 2018). In addition to cognitive deficits, Fragile X patients are associated with hypersensitivity to sensory stimuli and social deficits. Hypersensitivity to sensory stimuli is thought to underlie delayed maturation of the somatosensory cortex, seizures, and deficits in social interactions. Our findings indicate that autophagy is impaired in somatosensory cortex neurons of Fragile X mice and that activation of autophagy rescues hypersensitivity to sensory stimuli and social deficits in Fragile X mice.

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Nanosymposium

103. Behavioral Analysis of Developmental Disorders

Location: Room S403

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 103.12

Topic: A.07. Developmental Disorders

Support: Deborah Munroe Noonan Memorial Research Fund O'Brien Award
Research to Prevent Blindness /Lions Club International Foundation
NIH Grant EY019924-08

Title: Altered kurtosis in areas of white matter injury in adolescents with periventricular leukomalacia

Authors: *C. M. BAUER[1], B.-B. KOO[2], E. S. BAILIN[1], L. B. MERABET[3];
[1]Harvard Med. School, Massachusetts Eye and Ear, Boston, MA; [2]Boston Univ. Sch. of Med., Boston, MA; [3]Harvard Med. School; Massachusetts Eye and Ear, Boston, MA

Abstract: Background: Periventricular leukomalacia (PVL) commonly occurs in individuals born preterm, causing damage to the developing pre-oligodendrocytes and an initial decrease in myelination. It is unclear whether the observed dysmyelination continues throughout adolescence and into adulthood. It is possible that compensatory neuroplastic mechanisms enable the white matter to repair itself. The current study utilized diffusion kurtosis imaging (DKI) determine whether altered white matter myelination and micro-structural complexity persists in adolescents with PVL.
Methods: DKI data were acquired from a cohort of 8 participants (4 PVL and 4 controls) on a 3T Philips Achieva. DKI data were corrected for motion and eddy current distortion using the eddy correction tool in FSL (FMRIB Software Library, Oxford, UK) and then processed using the Diffusion Kurtosis Estimator (https://www.nitrc.org/projects/dke/) with a nonlinear least squares fit, minimum kurtosis = 0, C = 3, and a Gaussian kernel size of 3.375mm. These constraints ensure that the diffusivities and kurtosis values remain within a physically and biologically plausible range. Differences in kurtosis within the white matter were compared between individuals with PVL and typically-developing controls.
Results: Our results suggest that PVL is associated with significant changes in mean kurtosis (MK) in periventricular white matter that persist into adulthood. Specifically, significant increases in MK were observed in the left inferior parietal ($mean_{PVL} = 1.28 \pm 0.03$, $mean_{control} = 1.01 \pm 0.14$), left lateral occipital ($mean_{PVL} = 1.29 \pm 0.03$, $mean_{control} = 0.96 \pm 0.18$), and frontal pole ($mean_{PVL} = 1.20 \pm 0.03$, $mean_{control} = 0.93 \pm 0.12$), as well as the right caudal anterior cingulate ($mean_{PVL} = 1.21 \pm 0.02$, $mean_{control} = 0.96 \pm 0.14$) and cuneus ($mean_{PVL} = 1.26 \pm 0.02$, $mean_{control} = 0.99 \pm 0.12$) ($p < 0.05$).
Discussion: We observed regional increases in MK in individuals with PVL compared to controls. Previous studies indicate that decreased MK may represent thinner myelin sheaths, less dense axonal packing, neuronal shrinkage, or degenerative changes. Based on our findings, is it possible that the myelination process may thus be able to recover to some extent following early hypoxic-ischemic injury to the developing white matter. This study provides the opportunity to better understand the long-term consequences of neonatal damage to the developing white matter.

Disclosures: C.M. Bauer: None. **E.S. Bailin:** None. **L.B. Merabet:** None. **B. Koo:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.01

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

Support: Ellison Medical Foundation
Overland Foundation to NCS

Title: Phencyclidine-induced neurotransmitter switching in the mouse prelimbic cortex and its behavioral outcomes

Authors: *M. PRATELLI, N. C. SPITZER;
Neurobio. Section, Div. of Biol. Sciences, Kavli Inst. for Brain & Mind, UCSD, San Diego, la Jolla, CA

Abstract: The proper function of brain circuits relies on the correct specification and modulation of neurotransmission. Environmental stimuli inducing sustained alteration in neuronal firing can induce neurons in the adult brain to lose the transmitter they were expressing and gain a new one, a process called neurotransmitter switching (NTS). It typically involves re-specification from an excitatory to an inhibitory transmitter or vice versa, and has the potential to significantly impact the functioning of the neuronal circuits in which the neurons are involved. Subchronic treatment with phencyclidine (PCP) has been widely used as a pharmacological mouse model of schizophrenia. Alterations in neuronal activity and/or in GABAergic and glutamatergic neurotransmission have been repeatedly reported in the prelimbic cortex (PrL) of rodents exposed to PCP. However the relevance of NTS to the consequences of PCP exposure and to schizophrenia has not yet been explored. We find that PCP (10 mg/kg subcutaneously once a day for 10 days) induces a decrease in the number of vGluT1+ neurons and a concomitant increase in the number of GABAergic neurons in the mouse PrL, as revealed by stereological quantification. Combining a vGluT1::Cre transgenic line with a Cre-dependent TdTomato reporter, we show that the gain of GAD67 occurs specifically in glutamatergic neurons, suggesting that NTS is occurring. Subchronic PCP also induces alterations in behaviors that are modulated by multiple brain regions, including the PrL. We detect long term-memory deficits in the novel object recognition test, working memory impairments in the spontaneous alternation task, and sensitization to the acute locomotor effect of the drug. We now want to determine whether the glutamate-to-GABA NTS observed in the PrL of PCP-treated mice is causally linked to behavioral alterations. To override the NTS and assess behavioral rescue, we are stereotaxically injecting the PrL of vGluT1::Cre mice with a Cre-dependent AAV-GFP-GAD1-ShRNA viral vector. Evaluation of its ability to interfere with NTS and recover normal behaviors is in progress. If GAD1 down-regulation fails to rescue behaviors, a Cre-dependent AAV-mRuby-vGluT1 virus will be coinjected to more completely override the switch.

Disclosures: M. Pratelli: None. **N.C. Spitzer:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.02

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

Support: Fondation Fyssen postdoctoral fellowship
F30 DA40996
R01 DA35821
NS95809
P01 DA10154

Title: Different endocytic pathways make synaptic vesicles that store different neurotransmitters and release them with distinct properties

Authors: *K. SILM[1], J. YANG[1], P. F. MARCOTT[2], C. S. ASENSIO[1], J. ERIKSEN[1], D. A. GUTHRIE[3], A. H. NEWMAN[3], C. P. FORD[4], R. H. EDWARDS[1];
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Abstract: While synaptically acting neurotransmitters like glutamate and GABA convey precise information about timing, neuromodulators like monoamines signal changes in firing rate through bulk extracellular neurotransmitter concentration. These two modes of signaling require different mechanisms for release and are thought to reflect the properties of different cell types. Increasing evidence, however, indicates the use of multiple transmitters by individual neurons, raising questions about their mode of signaling. Focusing on neurotransmitter corelease from midbrain dopamine neurons, we show that vesicular transporters for monoamines (VMAT2) and glutamate (VGLUT2) segregate to different synaptic vesicles in slices as well as in cultured neurons. Analysis of dopamine neurons by live imaging and electrophysiology shows that dopamine and glutamate release differ in probability, coupling to presynaptic Ca^{++} channels and frequency dependence. Furthermore, the loss of clathrin adaptor protein AP-3 in *mocha* mice specifically affects the targeting and recycling of VMAT2 without affecting VGLUT2. Dopamine- and glutamate containing vesicles thus form through distinct recycling pathways within the same neuron and the two neurotransmitters are stored in vesicles with different identity. This enables coreleasing neurons to transmit two distinct signals, each of which conveys different information.

Disclosures: K. Silm: None. **J. Yang:** None. **J. Eriksen:** None. **C.S. Asensio:** None. **R.H. Edwards:** None. **D.A. Guthrie:** None. **A.H. Newman:** None. **P.F. Marcott:** None. **C.P. Ford:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.03

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

Support: Swedish Research Council 2015- 03359
Swedish Brain Foundation FO2016-0007
Längmanska kulturfonden BA17-0390

Title: Large scale analysis of the diversity and complexity of the adult spinal cord neurotransmitter typology

Authors: *A. PEDRONI, K. AMPATZIS;
Neurosci., Karolinka Institutet, Stockholm, Sweden

Abstract: The development of nervous system atlases is a fundamental pursuit in neuroscience, since they constitute a fundamental tool to improve our understanding of the nervous system and behavior. As such, neurotransmitter maps are valuable resources to decipher the nervous system organization and functionality. We present here the first comprehensive quantitative map of neurons found in the adult zebrafish spinal cord. Our study overlays detailed information regarding the anatomical positions, sizes, neurotransmitter phenotypes, and the projection patterns of the spinal neurons. We also show that neurotransmitter co-expression is much more extensive than previously assumed, suggesting that spinal networks are more complex than first recognized. As a first direct application of this atlas, we investigated the neurotransmitter diversity in the putative glutamatergic V2a interneuron assembly of the adult zebrafish spinal cord. These studies shed new light on the diverse and complex functions of this important interneuron class in the neuronal interplay governing the precise operation of the central pattern generators.

Disclosures: A. Pedroni: None. **K. Ampatzis:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.04

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

Support: Ellison Medical Foundation
Overland Foundation

Title: Role of transmitter plasticity in the development of PTSD

Authors: *H. LI, N. C. SPITZER;
Neurobio. Section, Div. of Biol. Sci., UC San Diego, Kavli Inst. for Brain and Mind, La Jolla, CA

Abstract: Post-traumatic stress disorder (PTSD) is a mental illness that is triggered by extreme traumatic stressors. A shift in excitatory to inhibitory (E/I) balance has been observed in PTSD patients (Trousselard et al., 2016; Frick et al., 2016) and may play a role in the development of PTSD. Neurotransmitter switching, a newly appreciated form of neuroplasticity, regulates E/I balance (Spitzer, 2017) and is thus an interesting candidate to be involved. In the present study we discovered in adult mice that a subset of serotonergic neurons of the lateral wings of dorsal raphe have switched their co-transmitter from glutamate/vGluT3 (vesicular glutamate transporter type 3) to GABA/GAD67 (glutamic acid decarboxylase 67) two weeks after intense foot-shock stress. At this time mice showed PTSD-like behaviors that included enhanced fear response, anxiety, hyperarousal and reduced sensorimotor gating. Both the transmitter switch and PTSD-like phenotypes caused by the acute foot-shock stress lasted for at least 1 month. Exposure to predator odor stress triggered the same switch in transmitters and generated PTSD-like behaviors, although to a lesser extent. To determine whether the switch takes place in the same neurons, we are now using a knock-in vGluT3-Cre mouse line crossed with a Rosa-TdTomato reporter line to permanently label vGluT3+ neurons with TdTomato and ascertain whether the loss of vGluT3/glutamate and the gain of GAD1/GABA both occur in TdTomato+ neurons. At the same time, to test whether the transmitter switch leads to the generation of PTSD-like behaviors, we are using Cre-dependent adeno-associated viruses (AAVs) to express exogenous vGluT3 and/or suppress expression of GAD1 in vGluT3 neurons that are expected to lose vGluT3 and gain GAD1. These experiments will determine whether overriding the switch affects the generation of some if not all of the PTSD-like behaviors. To determine the role of transmitter switching in preventing/treating PTSD, we are testing whether extinction therapy combined with fluoxetine administration prevents/rescues PTSD-like symptoms by regulating transmitter switching. This study is expected to promote understanding of the etiology of PTSD and provide new directions for developing therapeutic tools.

Disclosures: H. Li: None. **N.C. Spitzer:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.05

Topic: B.07. Synaptic Plasticity

Support: NIH-NIA K99AG059834

NIH-NIDA R01036612
NIH-NINDS R21NS087496
FWF-J3656-B24

Title: A role for VGLUT2 in the selective vulnerability of dopamine neurons in Parkinson's disease

Authors: *T. STEINKELLNER[1], T. S. HNASKO[2];
[1]Neurosciences, UCSD, La Jolla, CA; [2]Neurosciences, Univ. of California San Diego, La Jolla, CA

Abstract: Degeneration and dysfunction of midbrain dopamine (DA) neurons play a causal and contributing role in Parkinson's disease (PD). Although other neuron types are also affected, the cardinal symptoms of PD are a consequence of progressive DA neurodegeneration in the substantia nigra *pars compacta* (SNc). The precise mechanisms underlying DA neuron vulnerability remain unclear, but include mitochondrial dysfunction, oxidative stress, and α-synuclein aggregation. More recently, a glutamate-driven process has been implicated in disease progression, and there is now definitive molecular and physiological proof that DA neurons themselves express the vesicular glutamate transporter VGLUT2 and co-release glutamate. Further, there is evidence for a presynaptic role of VGLUT2, whereby VGLUT2 can increase the vesicular driving force for loading DA into synaptic vesicles, especially at times of high metabolic demand. This may enable tuning of DA release in response to activity changes. More recently, we discovered that >90% of SNc DA neurons express VGLUT2 in development, but most shut down VGLUT2 transcription in the adult. Interestingly though, VGLUT2 can re-emerge in response to neuronal insult by neurotoxins or in α-synuclein models. Re-emergent VGLUT2 expression may provide a beneficial compensatory adaptation for example through sequestration of endogenous or exogenous neurotoxins, and may contribute to the native resistance of ventral tegmental area (VTA) DA neurons that express more VGLUT2. Consistent with this, we find that midbrain DA neurons are more sensitive to neurotoxin-induced cell death in conditional knockout mice that lack VGLUT2 in DA neurons. On the other hand, we find that ectopic expression of VGLUT2 causes profound and selective toxicity to SNc DA neurons *in vivo* contingent on expression levels. Overall, our findings suggest that VGLUT2 expression in DA neurons is dynamically regulated, and that the balance of VGLUT2 expression has important consequences on DA neuron survival *in vivo*. We thus speculate that VGLUT2 expression is actively repressed in adult SNc DA neurons, de-repressed with injury and that dysregulated VGLUT2 expression contributes to DA neuron vulnerability in human PD.

Disclosures: T. Steinkellner: None. **T.S. Hnasko:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.06

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

Support: NIDA R01 DA038966

Title: Psychostimulant modulation of dopamine neuron connectivity to striatal cholinergic interneurons

Authors: *S. ZTAOU[1], N. CHUHMA[1], S. OH[1], M. MATAMALES[2], J. BERTRAN-GONZALEZ[2], S. RAYPORT[1];
[1]Dept. of Psychiatry, Columbia Univ., New York, NY; [2]Decision Neurosci. Lab., Univ. of New South Wales, Sydney, Australia

Abstract: Dysregulation of midbrain dopamine (DA) neuron projections to the striatum (STR) figures prominently in the pathophysiology of neuropsychiatric disorders. Psychostimulants, such as amphetamine (AMPH), target DA neuron synapses, potentially altering connectivity to engender drug dependent behaviors. However, it has been challenging to assess how AMPH exposure specifically alters DA neuron synaptic connectivity. We are addressing this using an optogenetic strategy that enables systematic recording of DA neuron connections, specifically how DA neuron burst firing affects the activity of STR neurons. Previously we showed that DA neuron glutamatergic synaptic connections to cholinergic interneurons (ChIs) in the nucleus accumbens medial shell (NAC mShell) are weakened 2.5 hours after AMPH injection. Now, we have investigated longer-term alterations, 24 hours after AMPH. Adult mice received low (2 mg/kg) or high dose (16 mg/kg) AMPH, or saline, and monitored for locomotor activity and stereotypy, associated respectively with the two AMPH doses. First, we evaluated the subregional impact of AMPH on ChI activity based on levels of the phosphorylation of ribosomal protein S6 (p-rpS6). AMPH attenuated ChI activity in STR subregions: low dose affected the NAC core and shell; high dose AMPH affected lateral (ldSTR) and medial dorsal STR (mdSTR).To elucidate AMPH effect on DA neuron synaptic connection, we performed whole-cell current clamp recordings from ChIs in slices from three distinct regions (NAC mShell, ldSTR, and mdSTR) 24 hours after AMPH. Low dose of AMPH attenuated the burst in NAC mShell ChIs, mediated by ionotropic glutamate receptors, and delayed burst in ldSTR ChIs, mediated by metabotropic glutamate receptors. However, no effects were observed in the mdSTR, region that does not show robust GLU cotransmission. These observations suggest that DA neuron GLU connections to ChIs are preferentially affected by psychostimulants, and they may be a crucial step in longer-term drug-induced plasticity in STR circuitry.

Disclosures: S. Ztaou: None. **N. Chuhma:** None. **S. Oh:** None. **M. Matamales:** None. **J. Bertran-Gonzalez:** None. **S. Rayport:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.07

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

Support: The Pittsburgh Foundation

Title: Novel roles for dynamic VGLUT expression in dopamine neurons in health and disease

Authors: D. ASLANOGLOU[1], M. VILLENEUVE[1], K. FOGLE[2], E. GEORGE[1], B. MCCABE[4], M. PALLADINO[5], C. E. CHEETHAM[3], ***Z. FREYBERG**[1];
[1]Psychiatry, [2]Pharm & Chem Bio, [3]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [4]EPFL, Lausanne, Switzerland; [5]Pharm & Chem Bio, Univ. Pittsburgh, Pittsburgh, PA

Abstract: The ability of presynaptic dopamine (DA) terminals to tune neurotransmitter release to meet the demands of neuronal activity is critical to neurotransmission. Although vesicle content was assumed to be static, we recently showed that cell depolarization increases synaptic vesicle DA content prior to release via vesicular hyperacidification. This depolarization-induced hyperacidification is mediated by the vesicular glutamate transporter (VGLUT) in both fly and mouse. These data suggest that in response to depolarization, DA vesicles utilize VGLUT to dynamically increase the vesicular pH gradient, thereby increasing dopamine vesicle content (Aguilar et al., Neuron 2017). We therefore hypothesized that the expression of VGLUT itself in DA neurons may also be dynamic. To test this, we developed a novel intersectional genetic reporter of VGLUT expression specifically in DA neurons in our *Drosophila* model. We found that the expression of *Drosophila* VGLUT (dVGLUT) in presynaptic DA neurons is indeed highly dynamic, particularly in response to changes in synaptic DA levels following treatments with amphetamine or reserpine. These data suggest that dVGLUT expressed in DA neurons may function as a sensor of local DA signaling to further tune vesicular content. Moreover, we also demonstrated that dVGLUT expression in DA neurons changes across the lifespan, decreasing throughout early adulthood, only to substantially increase in advanced age. Similarly, exposure to DA neuron-specific neurotoxins increased dVGLUT expression in the surviving DA neurons. Significantly, blocking increases in dVGLUT expression via RNAi knockdown made DA neurons more vulnerable to degeneration in the 6-OHDA model of Parkinson's disease. Our results demonstrate that changes in VGLUT expression may be a critical determinant of dopamine neuron survival in the settings of aging and/or cell stress/injury. Overall, these data provide new functional relevance to dopamine/glutamate co-transmission in both healthy and disease states.

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Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.08

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

Support: KIBM Grant #2018-1493

Title: Leptin receptor-expressing lateral hypothalamus mediates sustaining binge-like eating behaviors induced by early life trauma

Authors: *S. SHIN[1], C. R. LEE[1], X.-Y. WANG[1], B. LIM[2];
[2]Biol. Sci., [1]UCSD, La Jolla, CA

Abstract: Early life trauma (ELT) is a critical risk factor associated with binge eating behavior followed by the development of obesity in adulthood. However, neither the specific neural substrate nor the precise neural mechanisms underlying these processes are well-understood. Here, we found that mice exposed to ELT showed sustained binge-like eating behaviors and enhanced vulnerability to obesity in response to high fat diet (HFD), which is accompanied by down-regulation of leptin receptor (Lepr) signaling in the lateral hypothalamus (LH). Furthermore, after delivering adeno-associated virus expressing short hairpin RNA against Lepr in the LH, we observed that knockdown of Lepr signaling in the LH recapitulated the sustained binge-like eating behaviors as well as heightened sensitivity to weight gain in response to chronic HFD exposure. Using *in vivo* Ca^{2+} imaging, we found that enhanced activity of Lepr-expressing LH (Lepr LH) neurons was highly associated with sustained binge eating behaviors of ELT mice. Our results illustrate how Lepr LH neurons involved in obesogenic binge eating behavior induced by early adversity.

Disclosures: S. Shin: None. **B. Lim:** None. **X. Wang:** None. **C.R. Lee:** None.

Nanosymposium

104. Transmitter Co-Expression and Plasticity: From Health to Disease

Location: Room S104

Time: Sunday, October 20, 2019, 8:00 AM - 10:15 AM

Presentation Number: 104.09

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

Support: Boettcher Foundation

Title: Neurochemical signaling of reward and aversion in ventral tegmental area glutamate neurons using genetically-encoded GABA and glutamate sensors

Authors: *D. J. MCGOVERN[1], A. PHILLIPS[2], D. H. ROOT[3];
[1]Psychology and Neurosci., Universtiy Of Colorado Boulder, Boulder, CO; [2]Univ. of Colorado Boulder, Lafayette, CO; [3]Univ. of Colorado Boulder, Boulder, CO

Abstract: Genetically encoded fluorescent indicators, such as the calcium-sensor GCaMP, have advanced our understanding of how distinct brain structures and cell-types signal different aspects of motivated behavior. However, due to the slow timescale of neurotransmitter-identifying methods (i.e., microdialysis), identifying how specific neurotransmitters underlie neuronal activity dynamics during motivated behaviors has remained challenging. We utilized two recently-engineered genetically encoded fluorescent indicators to record the dynamics of glutamate and GABA transmission, the two primary neurotransmitters of the central nervous system, during motivated behavior. Using fiber photometry, glutamate transmission was recorded using SF-iGluSnFr and GABA transmission was recorded using iGABASnFr. The present work characterizes neurotransmitter specific inputs to ventral tegmental area glutamate neurons during aversive and rewarding tasks and compares these responses to firing patterns of VTA glutamate neurons during similar tasks. VGLUT2::CRE mice were initially trained to discriminate a CS+ that predicted sucrose reward from a CS- that did not predict reward. After learning, glutamate and GABA inputs to VTA glutamate neurons were recorded using fiber photometry. During the recording session, 10% of trials consisted of CS+ presentations that resulted in sucrose omission, as a measure of reward prediction error. Glutamate inputs to VTA glutamate neurons increased by the CS+, while GABA inputs to VTA glutamate neurons decreased. These results suggest that the increase in firing rate of VTA glutamate neurons at reward paired cues may result from direct activation or disinhibition. Both glutamate and GABA inputs to VTA glutamate neurons decreased at reward presentation. These results suggest that the decrease in firing rating recorded in these neurons at reward consumption could be due to global decreases in chemical signaling. Mice were subsequently trained on a Pavlovian paradigm in which a new CS+ proceeded footshock and a CS- predicted no shock. Glutamate inputs to VTA glutamate neurons increased at both the shock paired cue and shock presentation, while GABA inputs decreased at both the shock paired cue and shock. These results suggests that the increase in VTA glutamate neurons at aversive stimulus onset could be mediated by direct activation or via disinhibition. These findings provide novel insights into how glutamate and GABA inputs may modulate the firing patterns of VTA glutamate neurons during different motivated behaviors.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.01

Topic: C.01. Brain Wellness and Aging

Support: Kunin Professorship in Women's Healthy Brain Aging

Title: Human leukocyte antigen DRB1*13:02 protects against dementia

Authors: *L. JAMES[1], A. P. GEORGOPOULOS[2];
[1]Univ. of Minnesota/Minneapolis VAHCS, Minneapolis, MN; [2]Neurosci, Univ. Minnesota, Minneapolis, MN

Abstract: Human Leukocyte Antigen (HLA) class II genes play a critical role in immune protection from foreign antigens. Recent evidence documents protective effects of the HLA DRB1*13:02 allele, in particular, against age-related brain atrophy and neural network deterioration, suggesting a possible protection against dementia. Here we utilized a genetic epidemiological approach to investigate the association of DRB1*13:02 frequency and dementia prevalence globally. Results demonstrated that the prevalence of dementia decreases exponentially with increasing frequency of DRB1*13:02, even when adjusted for the prevalence of apolipoprotein E4 allele, a known risk factor for Alzheimer's disease. This finding documents the protective effect of DRB1*13:02 on dementia prevalence and implicates harmful persistent antigens as causal factors in the development of dementia.

Disclosures: L. James: None. **A.P. Georgopoulos:** None.

Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.02

Topic: C.01. Brain Wellness and Aging

Support: BBSRC DTP & University of Manchester studentship BB/J014478/1;
German Science Foundation Transregio-SFB 654 'Plasticity and Sleep';
Wellcome Trust ISSF award 105610/Z/14/Z.

Title: Susceptibility to auditory closed-loop stimulation of sleep slow oscillations changes with age

Authors: J. SCHNEIDER[1,2], *P. LEWIS[2], D. KOESTER[3], J. BORN[3], H.-V. NGO[4];
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Abstract: Cortical slow oscillations (SOs) and thalamo-cortical sleep spindles hallmark slow wave sleep and facilitate sleep-dependent memory consolidation. Experiments utilising non-invasive auditory closed-loop stimulation protocols to enhance these oscillations and associated cognitive processes have shown great potential in both young and older adults. However, the magnitude of the response has yet to be compared between these groups. Here, we directly compare the extent to which closed-loop auditory stimulation enhances SOs, fast spindles, and performance on memory tasks in young and older populations. In a within-subject design, subjects (n = 17, mean ± SEM = 55.7 ± 1.0 years, 9 female) received auditory closed-loop stimulation consisting of 50ms pink noise click sounds during SO up-states, which was compared to a control night without stimulation. Overnight memory consolidation was assessed for declarative word-pairs and procedural finger-tapping skill. Post-sleep encoding capabilities were tested using a picture recognition task. Additionally, electrophysiological effects of stimulation were compared to those reported previously in a younger cohort (n = 11, mean ± SEM = 24.2 ± 0.9 years, 8 female)[1]. We found that auditory stimulation prolonged endogenous SO trains and induced sleep spindles phase-locked to SO up-states in the older population). However, response amplitudes were markedly reduced compared to the younger subjects ($p < 0.05$). Furthermore, temporal dynamics of stimulation effects on SO and spindles differed between age groups, with SO peak power enhanced by stimulation only in young adults ($p < 0.001$), and fast spindle power only in older subjects ($p < 0.05$). Additionally, older adults generally demonstrated stronger fast spindle refractoriness ($p < 0.05$ and $p < 0.01$ in stimulation and control condition, respectively). Overnight retention and post-sleep encoding performance of the older cohort revealed no beneficial effect of stimulation, which instead impacted negatively on declarative post-sleep recall ($p < 0.05$). Our findings suggest that the susceptibility to auditory stimulation during sleep drastically changes with age and reveal the difficulties of translating functional protocols from younger to older populations.
References: [1] Ngo et al. (2013) Auditory Closed-Loop Stimulation of the Sleep Slow Oscillation Enhances Memory. *Neuron, 78 (3),* 545-553.

Disclosures: **J. Schneider:** None. **P. Lewis:** None. **D. Koester:** None. **J. Born:** None. **H. Ngo:** None.

Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.03

Topic: C.01. Brain Wellness and Aging

Support: This research was supported entirely by the Intramural Research Program of the NIH, National Institute on Aging.

Title: Magnetic resonance spectroscopy reveals age-related elevations in brain glucose

Authors: *R. J. MULLINS[1], D. A. REITER[2], D. KAPOGIANNIS[3];
[1]Natl. Inst. on Aging, Baltimore, MD; [2]Emory Univ. Sch. of Med., Atlanta, GA; [3]Natl. Inst. on Aging (NIA/NIH), Baltimore, MD

Abstract: In the global context of an aging population, it is crucial to understand the implications of brain metabolism abnormalities that occur with aging and Alzheimer's disease (AD). Emerging evidence points towards brain glucose hypometabolism as a common pathophysiological mechanism underlying aging, diabetes, and AD. In light of this, interventions such as intermittent fasting or ketogenic diets that aim to normalize or circumvent brain glucose metabolism are being investigated as treatments. We sought to assess changes in brain glucose metabolism over the course of normal human aging by directly measuring its concentration in vivo. We used an advanced two-dimensional magnetic resonance spectroscopy (MRS) technique called J-Modulated Point-Resolved Spectroscopy (J-PRESS), which allowed us to accurately measure metabolites elusive to one-dimensional MRS methods due to signal overlaps, such as glucose, glutamine, and glutamate. We performed J-PRESS MRS in 54 cognitively normal human participants ranging from 23 to 84 years of age (mean 55 +/- 18 yrs.). We obtained spectra from a single voxel placed within the precuneus because of its high resting metabolic activity and prior implication in cognitive decline with aging, AD and diabetes. We found that the precuneal glucose concentration (normalized to creatine) rises monotonically with increasing age ($r = .41$, $p = .002$), as well as age-related changes in other key brain metabolites. Specifically, precuneal levels of the neurotransmitter glutamate were lower in older participants ($r = -.46$, $p < .001$) while its precursor glutamine was higher ($r = .28$, $p = .04$), a result consistent with prior evidence for age-related imbalance in the glutamine-glutamate cycle. The glial cell marker Myo-inositol ($r = -32$, $p = .020$) and cell membrane component phosphocholine ($r = -.32$, $p = .019$) were both lower in older participants. This is the first in vivo study to quantify this expanded set of J-PRESS brain metabolites in normal aging, and convincingly demonstrates elevations in brain glucose over the course of normal aging. Previously, we had shown that brain glucose concentration is even higher in AD compared to age-matched subjects. These results suggest a continuum between age-related and AD-related changes in brain glucose metabolism. We propose non-invasive MRS-measured glucose as a means to characterize the interplay between glucose metabolism and age or disease-related cognitive decline, as a diagnostic biomarker for brain aging and AD, and as a therapeutic response biomarker for interventions targeting brain glucose metabolism.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.04

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG032289
Hillblom Network for the Prevention of Age-Associated Cognitive Decline

Title: Domain-specific functional network connectivity as a neural substrate of cognitive resilience in the aging brain

Authors: *S. M. WALTERS[1], K. B. CASALETTO[1], M. YOU[1], D. COTTER[1], M. ALTENDAHL[1], N. DJUKIC[1], S. WEINER-LIGHT[1], A. WOLF[1], Y. COBIGO[1], J. BROWN[1], C. A. LINDBERGH[1], H. ROSEN[1], A. APPLE[1], J. KRAMER[1], A. M. STAFFARONI[2];
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Abstract: Age-related declines in cognition are associated with decreases in grey matter volume (GMV), though significant divergence can exist between performance and brain structure. Some older adults outperform their peers despite similar GMV atrophy, a discrepancy conceptualized as “cognitive resilience”. While sociobehavioral measures are often used as proxies, less is known about the neural correlates of this phenomenon. Whole-brain functional connectivity (FC) has been proposed as a potential resilience mechanism. Little is known, however, about how FC in intrinsic brain networks could support resilience in specific cognitive functions. We investigated the moderating role of network-specific FC on the relationship between network volume and associated cognition in typically aging adults across three domains: executive functions (EF), processing speed, and episodic memory.

305 functionally normal older adults (age M=70.3; 57% female; education M=17.3; CDR=0) completed a neuropsychological battery, including EF, processing speed, and episodic memory, and underwent a brain MRI within 6 months. Mean connectivity of executive, subcortical, and default mode (DMN) networks was assessed using task-free fMRI and grey matter network volumes were extracted. Linear regression was used to investigate the interaction between network FC and volume on performance in each corresponding cognitive domain, covarying for age and gender. Sensitivity analyses additionally adjusted for total intracranial volume (TIV), GMV, whole-brain FC, and the moderating role of education on network volume, a well-established proxy of resilience.

Executive network FC moderated the relationship between executive network volume and EF (β=-.224, $p<.0001$) and remained significant after covarying for TIV, GMV, whole-brain FC, and the moderating effect of education (β=-.226, $p<.0001$). The relationship between EF network volume and EF performance attenuated with greater EF network FC. Subcortical FC was not a significant moderator of the relationship between subcortical network volume and processing speed ($p=.34$), nor did DMN FC moderate the association between DMN volume and memory ($p=.49$).

Higher FC within the EF network appears to support EF performance despite EF network volume loss in aging adults, independent of global brain volume and FC. Moreover, this effect remained significant after controlling for a moderating effect of education, a well-studied proxy of cognitive resilience. This study provides novel evidence that there may be network-specificity

to cognitive resilience in typical aging, and supports functional connectivity as an underlying neural substrate.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.05

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant 5R37AG-006265
NIA Grant RC1AG036199

Title: Brain activity differences between successful and unsuccessful agers

Authors: *X. CHEN, D. C. PARK;
Ctr. For Vital Longevity, Univ. of Texas At Dallas, Dallas, TX

Abstract: Background: Aging is often characterized by cognitive decline across the adult lifespan. Yet there is substantial variability in cognitive aging trajectories, with some individuals showing minimal decline and some showing rapid decline. The current study aims to identify successful agers who resist age-related decline in the Dallas Lifespan Brain Study, and compare the brain activity between successful and unsuccessful agers. **Methods**: A total of 232 participants aged 35-89 years old at baseline completed two waves of longitudinal memory measurement with a four-year interval, as well as a subsequent memory fMRI task in the second wave of testing. Participants' cross-sectional performance level and longitudinal cognitive change in episodic memory were estimated using latent difference score model. Then, participants were divided into three age groups (Middle: 35-54; young-old: 55-69; old-old: 70-89), and successful agers were defined as individuals with better than average performance level and slower than average change rate in the age group, vice versa for unsuccessful agers. The brain activity of subsequent memory effect (high-confidence remember > forget) in task-related regions was compared between successful and unsuccessful agers. **Results**: A total of 90 unsuccessful agers and 95 successful agers were identified. In the subsequent memory fMRI task, participants overall activated bilateral fusiform/parahippocampal areas and bilateral middle occipital regions during encoding of successfully remembered items. ROI analyses using these clusters found that successful memory aging in young-old individuals was related to preserved activation in these temporal-occipital regions, particularly in right middle occipital cluster and

left fusiform/parahippocampal cluster. **Conclusions**: Young-old individuals may rely on the ability to maintain brain function, despite aging, to achieve successful cognitive aging. Old-old adults, on the other hand, barely had any task-related activity suggesting the limited brain maintenance in those aged brains. Future study may explore longitudinal change in functional activation and directly track the brain functional development in successful and unsuccessful agers.

Disclosures: X. Chen: None. **D.C. Park:** None.

Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.06

Topic: C.01. Brain Wellness and Aging

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OCNS

Title: BDNF enhances synaptic function in Munc18-1 deficient neurons

Authors: Y. I. LEE[1], A. OROCK[2], Y. G. KIM[1], K. M. JOO[3], S. LOGAN[4], A. LORINCZ[6,7], ***F. DEAK**[5,7];
[1]Anat., Dankook Univ., Cheonan, Korea, Republic of; [2]Oklahoma Ctr. for Neurosci., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [3]Single Cell Network Res. Ctr., Sungkyunkwan Univ. Sch. of Med., Suwon, Korea, Republic of; [4]Reynolds Oklahoma Ctr. on Aging/Geriatric Med., [5]Geriatric Med., Univ. of Oklahoma HSC, Oklahoma City, OK; [6]Florida State Col., Jacksonville, FL; [7]Neurosci., Mayo Clin., Jacksonville, FL

Abstract: Brain derived neurotrophic factor (BDNF) has a central role in maintaining and strengthening neuronal connections and to stimulate neurogenesis in adult brain. Decreased levels of BDNF in the aging brain are thought to usher cognitive impairment. BDNF is stored in dense core vesicles and released through exocytosis from the neurites. There is a mutual positive correlation between BDNF secretion and synaptic activity as BDNF secretion requires strong neuronal activation and it depends on dendritic calcium signal. The exact mechanism for the regulation of BDNF secretion is not well understood. It is assumed to be stored in vesicles and released through exocytosis from the dendrites. Munc18-1 (STXBP1) was found to be essential for the exocytosis of synaptic vesicles, but its involvement in BDNF secretion is not known.

Interestingly, neurons lacking munc18-1 undergo severe degeneration in newborn mice. Here we report the effects of BDNF treatment on the presynaptic terminal using munc18-1 deficient neurons. Reduced expression of munc18-1 in heterozygous neurons (+/-) diminishes synaptic transmitter release, as tested here on individual synaptic connections with FM1-43 fluorescence imaging. Transduction of cultured neurons with BDNF markedly increased BDNF secretion in wild-type but was less effective in munc18-1+/- cells. In turn, BDNF enhanced synaptic functions and restored the severe synaptic dysfunction induced by munc18-1 deficiency. The role of munc18-1 in the synaptic effect of BDNF is highlighted by the finding that BDNF upregulated the expression of munc18-1 in neurons, consistent with enhanced synaptic functions. Accordingly, this is the first evidence showing the functional effect of BDNF in munc18-1 deficient synapses and about the direct role of munc18-1 in the regulation of BDNF secretion. We propose a molecular model of BDNF secretion and discuss its potential as therapeutic target to prevent cognitive decline in the elderly.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.07

Topic: C.01. Brain Wellness and Aging

Support: FCT, Portugal (POCI-01-0145-FEDER-030786)
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(CENTRO-01-0145-FEDER-000012: HealthyAging2020)
(CENTRO-01-0145-FEDER-000008: BrainHealth 2020)

Title: Emotions, neurochemistry and circulating extracellular vesicles: These all come with chronic aerobic physical exercise

Authors: *F. C. PEREIRA[1], M. RODRIGUES[1], J. REIS[1], E. SOARES[1], H. FERREIRA[1], I. PITA[1], S. VIANA[1,4], C. LEMOS[5], N. LIMA[2], T. S. MARTINS[6], J. CATITA[7,8], A. G. HENRIQUES[6], M. ZUZARTE[3], T. MARTINS-MARQUES[3], T. RIBEIRO-RODRIGUES[3], H. GIRÃO[3], A. S. AGUIAR, JR[9], C. A. FONTES-RIBEIRO[1];
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Abstract: Rational: Lifelong aerobic physical exercise (PE) is a promising preventive or disease-modifying strategy in brain pathologies, including emotional and degenerative disorders. However, the biological mediators of the beneficial effects of PE have not been fully elucidated. Recently, it was shown that acute aerobic PE induced a rapid release of extracellular vesicles (EVs) into the circulation in men. This heterogenous group of small lipid-enclosed structures is a powerful mediator of cell-cell communication. **Aims:**Herein we characterized the emotional, neurochemical and circulating extracellular vesicles signature of a chronic aerobic exercise**. Methods:**Young-adult male C57BL/6 mice (8 weeks-old) were subjected to an incremental treadmill PE program (five days a week for eight weeks; slope of 8.7%). The sedentary animals were placed daily on the switched-off treadmills during the exercise time. Mice emotional status was monitored at the 4thand 8thweek of exercise. Animals were sacrificed 10 min-post PE protocol, and blood, spleen, heart and striata and frontal cortices were collected. Serum-derived EVs were isolated and evaluated by Western Blotting (WB), transmission electron microscopy (TEM) and by nanoparticle tracking analysis (NTA). Physiological parameters including circulating corticosterone were evaluated. A detailed neurochemical profile that includes glucocorticoid receptors (GR), RAGE and TLR-7 (immune markers), GFAP and alpha-synuclein density evaluation by WB is provided. Data are presented as mean ± standard error of the mean (SEM). Groups (SED and EXE, n=8) were compared using a student's t-test. Differences were considered to be significant at $p<0.05$. **Results:**PE induced a reduction in spleen and an increase in circulating corticosterone ($p<0.05$), which is suggestive of a stress-response. However, PE did not impose any changes in emotional behavior as assessed by open field test, tail suspension test, splash test, elevated plus maze and light/dark box transition test. Consistently, all the striatal and frontal cortical neurochemical markers were not significantly changed by the PE protocol. Importantly, our study revealed for the first time that chronic PE seems to increase the number of circulating EVs (size and morphology were analysed by TEM and NTA) in mice. These EVs were positive for CD63 and CD81 (exosomal markers, WB). **Conclusion:** Chronic treadmill exercise impacts circulating EVs without changing emotional parameters. The role of PE-triggered EVs needs to be studied.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.08

Topic: C.01. Brain Wellness and Aging

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The Family Knut and Alice Wallenberg Foundation

Title: On apolipoprotein CIII in the central nervous system

Authors: *I. V. ACEBES, P. RECIO-LÓPEZ, P.-O. BERGGREN, L. JUNTTI-BERGGREN; Mol. Med. and Surgery (MMK), Karolinska Institutet, Stockholm, Sweden

Abstract: Apolipoprotein CIII (apoCIII) is a pro-inflammatory lipoprotein which increases in obesity and diabetes mellitus (DM). Extensive research has been performed to connect certain apolipoproteins with neurological and psychiatric disorders. However, the presence of apoCIII in the central nervous system (CNS) and its relationship to brain disorders have never been investigated. We hypothesize that apoCIII is present in different areas of the CNS and that brain apoCIII is as an inducible factor that increases upon diet-induced obesity (DIO) and type-2 DM (T2DM). To test our idea we used 22-week old male C57Bl6/j (B6) mice and performed immunohistochemical (IHC) studies in formalin-fixed brain cryosections by using a specific antibody against mouse apoCIII (*n=3*). To confirm the presence of apoCIII in the mouse brain, we used 22-week old male *APOC3*-deficient mice (*APOC3*$^{-/-}$) and their corresponding heterozygous (*APOC3*$^{+/-}$) and wild-type (*APOC3*$^{+/+}$) littermates. In this mouse model, fresh frozen brains were microdissected *in loco* and CNS mapped for apoCIII gene expression by quantitative Real-Time polymerase chain reaction (qRT-PCR) (*n=4* in duplicate). Finally, to examine whether DIO and T2DM change apoCIII levels within the mouse CNS, we used 8-week old male B6 mice fed either a chow or a high-fat diet (HFD) for 14 weeks. At the end of the diet studies, apoCIII levels were determined in different brain areas by qRT-PCR and immunoblot (*n=6*). Our exploratory IHC results revealed that apoCIII is present in the medial prefrontal cortex (mPFC), the nucleus accumbens, the amygdala and the thalamus. In the hippocampus, we found that apoCIII is present in the *stratum pyramidale* and, to a lesser extent, in the *stratum oriens* and the *stratum radiatum*. In the hypothalamus, apoCIII is predominantly present in the arcuate nucleus and the lateral hypothalamic area. Results from IHC on brain apoCIII were confirmed in the same brain areas at the gene expression level in *APOC3*$^{+/+}$ mice. Moreover, brain apoCIII was 2-fold decreased in *APOC3*$^{+/-}$ in the above mentioned brain areas, and not detectable in *APOC3*$^{-/-}$. Finally, obese and diabetic HFD-fed B6 mice significantly increased apoCIII, both at the gene and at the protein level, in the mPFC, the hippocampus, the hypothalamus and the pituitary gland, as compared to chow-fed controls. In conclusion, we have identified the presence of apoCIII in the mouse brain and we provide evidence that locally produced brain apoCIII is an inducible factor under obesogenic/diabetogenic conditions. These

findings suggest that brain apoCIII can potentially constitute a druggable target in the battle against brain disorders linked to metabolic diseases.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.09

Topic: C.01. Brain Wellness and Aging

Support: NIMH-NIH T32 Grant MH067631-14

Title: Autophagosome-lysosome fusion is altered in the maternal murine brain across pregnancy

Authors: *R. A. SMITH, D. I. RAPOLTI, D. NGUYEN, E. R. BONGARZONE;
Anat. and Cell Biol., Univ. of Illinois at Chicago, Chicago, IL

Abstract: The perinatal period is a time of increased cognitive risk for women. One in seven women will develop postpartum mood disorders. Similarly, women with neurodegenerative disorders, such as multiple sclerosis, frequently experience symptom remission during pregnancy followed by rapid relapse during the postpartum period. While peripartum cognitive changes are frequently observed, relatively little is known about how pregnancy affects the brain at a subcellular level. Using a CAG-RFP-EGFP-LC3 transgenic mouse line, which allows visualization of lysosome and autophagosome fusion in the mouse brain without the need for immunohistochemistry, we quantified autophagosome-lysosome flux across pregnancy. We measured increased numbers of unfused autophagosomes in the medial prefrontal cortex (mPFC) and the hippocampus during the peripartum period. Subsequent western blotting revealed regional alterations in autophagosome and lysosome availability: the mPFC had an increased number of autophagosomes and lysosomes at the time of parturition, relative to the nulliparous state, while the hippocampus maintained a steady level of both autophagosomes and lysosomes from the nulliparous state through the postpartum period. These results suggest that autophagosome-lysosome fusion is differentially regulated in selected brain regions during the peripartum period; however, the mechanism driving these fusion changes remains unclear. Changes in autophagosome-lysosome degradation have been implicated in the development of several psychiatric disorders, including schizophrenia and major depressive disorder, thus our results provide a window of opportunity to understand the contribution of these changes in pregnancy-related psychiatric alterations. Further analysis of this pathway may elucidate the subcellular mechanisms of increased cognitive risk during the peripartum period.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.10

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 AG055449

Title: Cortical iron deposition predicts reduced working memory performance and decreased functional connectivity of working memory networks in older adults

Authors: *V. ZACHARIOU, C. E. BAUER, E. R. SEAGO, B. T. GOLD;
Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: The contribution of iron to brain function has a dual nature. On the one hand, iron is vital to cellular metabolism. On the other hand, excess iron accumulation leads to oxidative stress, which can interfere with neurotransmission, contribute to neurodegeneration and induce cognitive impairment. For instance, several previous studies have reported a negative association between iron concentration in subcortical brain regions, like the caudate and putamen, and working memory performance. Working memory, however, is subserved primarily by a network of cortical, rather than subcortical, brain regions that span frontal and parietal cortices. Whether cortical iron load affects this frontoparietal working memory network and, as a consequence, working memory performance, remains an open question. Here, we explored this question using quantitative susceptibility mapping (QSM), an in-vivo MRI technique for measuring iron concentration in brain tissue, in conjunction with task-based functional connectivity, in a cohort of cognitively normal older adults (n = 41; age range: 67-86). Participants performed an N-Back visual working memory task inside a 3T MRI scanner. Using whole-brain fMRI activity from this task, we identified a bilateral network of brain regions in which the magnitude of activity in response to the N-Back task significantly predicted task performance (dprime). These regions included the anterior cingulate cortex, the dorsolateral prefrontal cortex, the middle frontal gyrus and the inferior parietal lobules. Then, using each of these regions as a seed, the task-based functional connectivity of each region with every other region was calculated and subsequently correlated with QSM values (iron concentration in ppb) and working memory performance (dprime; controlling for age and gender). QSM values were extracted from individually defined gray matter lobar masks. We found that iron accumulation in the parietal lobe, within the context of the omnibus regression model, negatively predicted the degree of functional connectivity between the bilateral inferior parietal lobules and the rest of the seed ROIs ($p = 0.04$, Std. Beta =

-0.45, $r^2 = 0.22$). Crucially, the concentration of iron in the parietal lobe correlated negatively with working memory performance ($p = 0.006$, Std. Beta = -0.51, $r^2 = 0.17$). Iron accumulation in the other lobes did not affect functional connectivity or working memory performance. In sum, iron deposition in the parietal lobe predicts decreased working memory performance and reduced task-based functional connectivity of working memory networks in cognitively normal older adults.

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Nanosymposium

105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.11

Topic: C.01. Brain Wellness and Aging

Support: J J Mason and H S Williams Memorial Foundation Grant MAS2016F037

Title: Poly I:C and LPS induce blood-brain barrier disruption and fatigue behavioural phenotype in rodents *in vivo*

Authors: *L. M. LANDOWSKI, C. G. FOSTER, B. A. SUTHERLAND, D. W. HOWELLS; Sch. of Med., Univ. of Tasmania, Hobart, Australia

Abstract: Fatigue is an unrelenting state of weariness that is not relieved by rest, and is commonly associated with a variety of diseases and illnesses. Fatigue can be disabling and interfere with functional ability and quality of life. Despite 13-33% of patient visits to a GP citing fatigue as a primary complaint, no targeted treatment exists. The poor understanding of the physiological mechanisms underpinning fatigue remains the single most important limiting factor for developing efficacious treatments. Animal models are an excellent tool to study fatigue mechanisms and develop potential therapeutic strategies, however, they have not been fully characterised. Systemic-induced inflammation is commonly used to replicate the symptomology associated with fatigue. The systemic inflammatory-inducing molecules polyrinoinosinic:polyribocytidylic (poly I:C; 0.3, 3 and 4.5mg/kg) and lipopolysaccharide (LPS; 3mg/kg) were used to induce fatigue in this randomised and blinded study. There was significant modulation of activity (open field, overnight in-cage monitoring), and reward-seeking behaviour (sunflower seed test, sucrose preference test) in animals administered 3 and 4.5mg/kg poly I:C and LPS. Increased blood brain barrier permeability occurs in the hypothalamus of Poly I:C treated rodents, compared to control ($p<0.02$), as demonstrated by a significant decrease in fibrinogen vessel:tissue staining intensity. Administration of LPS induced a greater magnitude of weight loss and activity (open field) reduction compared to poly I:C, however the deficits of LPS occurred between days 3-5 post-injection compared to poly I:C, which occured between days 7-

11. Pyrexia was induced following poly I:C administration and resolved within 24 hours. Our results highlight that both poly I:C and LPS induce a behavioural phenotype similar to human fatigue and therefore are viable models of fatigue.

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105. Brain Aging and Role of Systemic Factors

Location: Room S405

Time: Sunday, October 20, 2019, 8:00 AM - 11:00 AM

Presentation Number: 105.12

Topic: C.01. Brain Wellness and Aging

Title: A transformational plasma-based approach to Alzheimer's disease therapeutics

Authors: *S. P. BRAITHWAITE, B. SZOKE, S. LOHR, J. HANNESTAD, S. MINAMI, V. KHEIFETS;
Alkahest, San Carlos, CA

Abstract: Alzheimer's Disease (AD) incidence is rapidly increasing as the world's population ages. Given the availability of only symptomatic options, there is a significant need to develop novel therapeutic strategies to slow the progression of the disease. As the major risk factor for development of AD is age, we have explored the possibilities of modulating fundamental biological processes of aging to treat AD. Utilizing plasma, and fractions of plasma, derived from healthy human donors, we have demonstrated that a multimodal reversal of aging processes can be achieved in the mouse brain, resulting in functional improvements including cognition. The relevance of these improvements in aged wild-type mice to the human AD state were assessed through both direct testing and correlational studies. In the brain, reductions in neuroinflammation, increases in synaptic density and neuronal activity, as well as long term changes in neurogenesis and neuronal survival were observed. In *in vitro* studies positive effects on neuronal properties and network activity were achieved. Deep analysis of the plasma proteome in both healthy aging and in the progression of Alzheimer's disease suggest that proteins in the plasma proteome can contribute to disease progression and that the modulation of the plasma proteome via infusion of plasma fractions can confer benefits. The therapeutic potential of this approach is being translated to human clinical testing with evaluation of the human plasma protein fraction GRF6019 in mild-moderate AD patients.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.01

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

Support: the Cure Alzheimer’s Fund
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Title: Sex-specific effects of microbiome perturbations on cerebral abeta amyloidosis and microglia phenotypes in an Alzheimer's transgenic mouse model

Authors: *H. B. DODIYA[1], T. KUNTZ[1], S. M. SHAIK[1], C. BAUFELD[2], J. LEIBOWITZ[2], X. ZHANG[1], N. GOTTEL[3], X. ZHANG[1], O. BUTOVSKY[2], J. A. GILBERT[3], S. SISODIA[1]; [1]Neurobio., Univ. of Chicago, Chicago, IL; [2]Neurology/ARCND, Brigham and Women's Hosp., Boston, MA; [3]Univ. of California San Diego, San Diego, IL

Abstract: <u>Background:</u> Using two separate transgenic (Tg) mouse models of Abeta amyloidosis, our group established a strong association between gut microbiome with cerebral amyloid- β (Aβ) plaque pathology and plaque-localized gliosis. Specifically, antibiotic (ABX) cocktail mediated perturbations of the gut microbiome was associated with reduced amyloid-β (Aβ) plaque pathology and altered plaque-localized microglia characteristics in male Tg mice of prion protein promoter driven $APP_{SWE}/PS1_{\Delta E9}$ and a highly aggressive Thy1 promoter driven $APP_{SWE}/PS1_{L166P}$ (APPPS1-21 line).

Method: To establish a causal relationship, we performed fecal microbiota transplantation experiments in long-term ABX-treated male APPPS1-21 mice. Furthermore to investigate the role of sex-specific microbiome, we also performed fecal transfer between ABX-treated APPPS1-21 male into female APPPS1-21 mice to check if female confer APPPS1-21 mice the similar beneficial effects as observed in ABX-treated male APPPS1-21. Histopathology, microglia phenotypic characteristics, brain transcriptome, peripheral cytokines and gut microbiota profiles were evaluated.
Result: Using our established ABX protocol, we found that ABX-treatment lead to perturbations of the microbiome. This alteration in microbiome was associated with a reduction in Aβ pathology and altered microglia phenotypes only in male mice. We observed reduced species diversity and similar microbiome profiles in both male and female mice immediately after postnatal ABX gavage, but interestingly, the microbiome profiles exhibited sex-specific differences by 7 weeks of age. While ABX treatment had a significant impact on microglial morphology in male mice at 7 weeks compared with vehicle-treated animals, we did not observe these microglial morphological alterations in female mice. Furthermore, ABX treatment led to pronounced alterations in inflammation-related transcripts in the male cortex compared with female mice. Finally, we demonstrate that fecal microbiota from 7-week-old transgenic APPPS1-21 male mice transplanted into ABX-treated male mice partially restored Aβ plaque pathology and microglial morphological phenotypes.
Conclusion: We conclude that the ABX-mediated perturbations of the gut microbiome lead to sex-specific influences on cerebral Aβ amyloidosis and microglial phenotypes in the APPPS1-21 mouse model further strengthening microbiota-gut-brain axis in Alzheimer's pathogenesis.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.02

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

Support: CIHR Project Grant PJT-364544

Title: Early intraneuronal amyloid triggers neuron-derived inflammatory signaling in APP transgenic rats and human brain

Authors: *L. WELIKOVITCH, S. DO CARMO, A. C. CUELLO;
McGill Univ., Montreal, QC, Canada

Abstract: Neuroinflammation in Alzheimer’s disease (AD) has classically been attributed to sustained glial activation in response to amyloid-β (Aβ) plaques and ongoing neurodegeneration. However, we now understand that the AD neuropathology develops silently for decades, well-before the onset of clinical symptoms. Moreover, NSAID-use during this asymptomatic period decreases the risk of AD, suggesting that inflammation is likely involved in the earliest stages of disease development. Our lab and others' have shown that neuroinflammation in transgenic rodent models begins months before extracellular plaque deposition, coincident with intraneuronal Aβ accumulation, microglial activation and cognitive deficits. We propose that this plaque-independent inflammatory reaction originates from neurons burdened with toxic intracellular Aβ during the earliest stages of the amyloid pathology. To evaluate the inflammatory gene expression-profile of Aβ-burdened neurons, we used laser capture microdissection to extract neurons from the hippocampus of pre-plaque McGill-R-Thy1-APP transgenic rats and subjected them to qRT-PCR. We quantified the neuronal expression of inflammatory molecules by performing neuron-specific fluorescence quantification following immunolabeling and RNA FISH. We demonstrate for the first time that Aβ-burdened neurons initiate a potent inflammatory signal driven by an upregulation in CCL2, CCL3 and IL-6 *before* Aβ plaque deposition. We also show that levels of neuron-derived cytokines correlate with the extent of microglial activation and mobilization, even in the absence of plaques and cell death. Moreover, we provide evidence that a similar neuron-specific inflammatory response may precede insoluble amyloid and tau pathologies within disease-vulnerable regions of the human brain. While low levels of intraneuronal Aβ can be detected in cognitively unimpaired individuals, our findings suggest that abnormally high intraneuronal Aβ unleashes a pro-inflammatory response, laying the groundwork for early synaptic disruptions and triggering the AD neuropathological cascade. Thus, we reveal the Aβ-burdened neuron as a primary pro-inflammatory agent, implicating the neuronal accumulation of soluble Aβ as a significant immunological component of the AD pathogenesis.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.03

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

Support: KAKENHI 18K07389

Title: HDAC3 inhibition ameliorates memory function via M2 microglia in a transgenic mouse model of Alzheimer’s disease

Authors: *T. KUBOYAMA, C. TOHDA;
Instit of Natural Medicine, Univ. of Toyama, Toyama, Japan

Abstract: Amyloid β (Aβ) skews microglia to M1 phenotype and induces inflammation and neurodegeneration. On the other hand, another type of microglia, M2, shows anti-inflammatory and neurotrophic effects. We previously clarified that HDAC3 inhibition induced predominance of M2 microglia and axonal growth, and recovered locomotor function in spinal cord injured mice. Therefore, this study aimed to clarify that HDAC3 inhibition skewed to M2 microglia and restored memory function in Alzheimer's disease model mice. In cultured microglia, a treatment with an HDAC3 inhibitor, RGFP966, skewed to M2 microglia when treated 24 h after Aβ addition. Conditioned medium was collected from RGFP966-treated microglia, which recovered Aβ-induced collapse of axonal growth cones. RGFP966 was intraperitoneally administered to 5XFAD mice, a transgenic model of Alzheimer's disease. RGFP966 decreased degenerated axons in Aβ plaques and improved novel object recognition memory. When microglia in the brain of 5XFAD mice were eliminated by intracerebroventricular administration of clophosome, the effects of RGFP966 were diminished. These results suggest that HDAC3 inhibition increased predominance of M2 microglia, recovered axonal degeneration, and ameliorated memory deficit in 5XFAD mice.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

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Presentation Number: 106.04

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

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Title: Gastrointestinal (GI) tract microbiome-derived, lipopolysaccharide (LPS)-mediated up-regulation of microRNA-146a in sporadic Alzheimer's disease (AD)

Authors: Y. ZHAO[1], V. R. JABER[2], N. M. SHARFMAN[2], W. LI[3], ***W. J. LUKIW**[4];
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Abstract: Background: The first evidence for a potential molecular-genetic and mechanistic link between the pathobiology of human gastrointestinal (GI)-tract microbiome-derived

lipopolysaccharide (LPS) and the inflammatory degenerative mechanisms of sporadic Alzheimer's disease (AD) came just 6 years ago [Bhattacharjee S, Lukiw WJ. Alzheimer's disease and the microbiome. Front Cell Neurosci (2013) doi:7:153.10.3389/fncel.2013.00153]. Accumulating evidence continues to strengthen the hypothesis that neurotoxic microbial-derived components of the GI tract microbiome (both viral- and bacterial-derived) can cross the aging GI tract and blood-brain barrier (BBB) and contribute to progressive pro-inflammatory neurodegeneration, as is typified by the AD-process. Method: Analysis, culture and extraction of *Escherichia coli*, *Bacteroides fragilis*, and other Gram-negative anaerobes; bioinformatic algorithms; collection and culture of human GI tract microbial species; DNA and RNA sequencing; LED-Northern dot blotting; microRNA- and messenger RNA (mRNA)-based microfluidic array analysis and profiling; quantitative and analytical RT-PCR and imunocytochemistry; viral assay and quantitation of HSV-1. Result: Of central interest in these recent investigations are the pathological roles played by human GI tract resident Gram-negative anaerobic bacteria and neurotropic viruses - two prominent divisions of GI tract microbiome-derived microbiota - which harbor considerable pathogenic potential. It is noteworthy that the first two well-studied microbiota - the neurotropic herpes simplex virus-1 (HSV-1) and the GI-tract abundant Gram-negative bacteria *Bacteroides fragilis* both share a final common pathway of NF-κB (p50/p65) activation and microRNA-146a induction with ensuing pathogenic stimulation of innate-immune and neuro-inflammatory pathways. These strongly contribute to the inflammatory, amyloidogenic and progressive neurodegenerative pathology of AD. Conclusion: The work in this paper: **(i)** expands recent research that has extended our understanding of the nature of the translocation of microbiome-derived neurotoxins-across biophysiological barriers; **(ii)** has assessed the induction of the pro-inflammatory pathogenic microRNA-146a by these two prominent classes of human GI-tract microbiota (HSV-1 and *B. fragilis*); and **(iii)** advances the role of molecular neurobiology and mechanistic contribution of polymicrobial infections to AD-type neuropathological change.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

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Title: TREM2 function impedes tau seeding in neuritic plaques

Authors: *C. E. LEYNS[1,2,3], M. GRATUZE[1,2,3], S. NARASIMHAN[5], N. JAIN[1,2,3], L. J. KOSCAL[1,2,3], M. MANIS[1,2,3], H. JIANG[1,2,3], M. COLONNA[4,2,3], V. M. Y. LEE[5], J. D. ULRICH[1,2,3], D. M. HOLTZMAN[1,2,3];
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Abstract: Variants in the triggering receptor expressed on myeloid cells 2 (TREM2) are associated with increased risk for sporadic, late-onset Alzheimer's disease (AD). Functional studies have shown that loss of TREM2 function impairs the microglial response to amyloid-β (Aβ) plaques which is correlated with increased peri-plaque neurite damage. Together, TREM2 genetic and functional studies suggest that plaque-associated microglia have an essential role in mitigating neuronal dystrophy inflicted by adjacent Aβ plaques. Yet, their impact on AD pathogenesis and how the TREM2 variants that hinder them contribute to AD risk and progression remains ambiguous. Here we show that germline knockout of *Trem2* or the *TREM2*^{R47H} variant reduce microgliosis around Aβ plaques and facilitate the seeding and spreading of neuritic plaque (NP) tau aggregates in mice. Furthermore, NP tau seeding was strongly correlated with the amount of $A\beta_{42}$ and neuronal dystrophy staining surrounding the plaques. Analysis of 15 case-controlled human AD cortical samples corroborated increased NP tau deposition in *TREM2*^{R47H} and *TREM2*^{R62H} variant carriers independent of apolipoprotein E ε4 genotype. These findings demonstrate a key role for TREM2 and microglia in limiting the development of peri-plaque tau pathologies. Our data further suggests that microglia and TREM2 lay at the critical intersection of Aβ and tau pathologies in AD and that loss of plaque-associated microglia in TREM2 variant carriers increases AD-risk and disease progression via increasing susceptibility to tau seeding and spread.

Disclosures: **C.E. Leyns:** A. Employment/Salary (full or part-time):; Merck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); WO 2016126993 A1. **M. Gratuze:** None. **S. Narasimhan:** None. **N. Jain:** None. **L.J. Koscal:** None. **M. Manis:** None. **H. Jiang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); WO 2016126993 A1. **M. Colonna:** None. **V.M.Y. Lee:** None. **J.D. Ulrich:** None. **D.M. Holtzman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); WO 2016126993 A1. F. Consulting Fees (e.g., advisory boards); AbbVie, Proclara, Denali, Genentech, Eli Lilly. Other; C2N Diagnostics.

Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.06

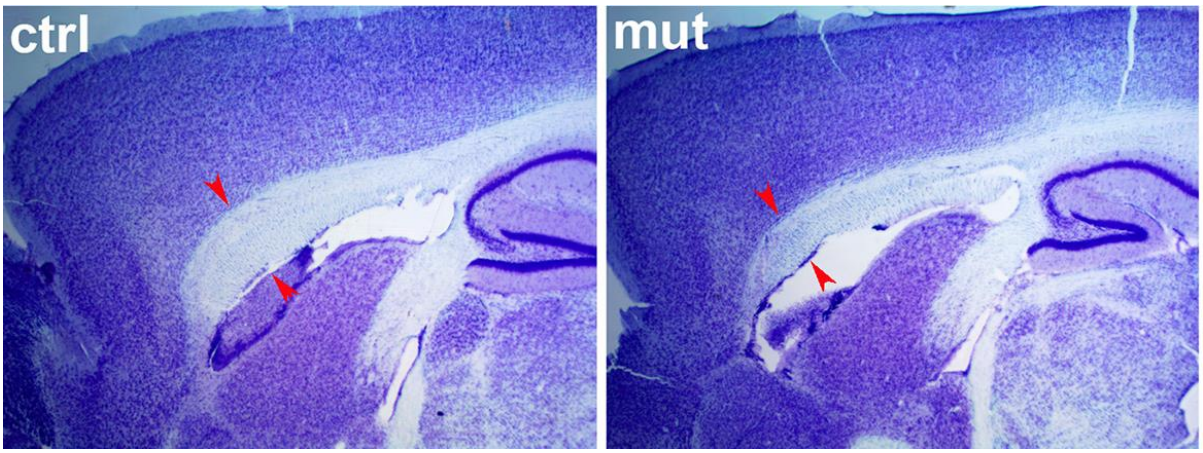
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: March of Dimes foundation

Title: Microglia-specific cytokine dysregulation results in Alzheimer’s disease-like plaques and tangles in mice

Authors: *Z. HUANG, H. KWON, D. SANTHOSH;
UW-Madison, Madison, WI

Abstract: Alzheimer’s disease (AD) has two tightly linked pathological hallmarks, amyloid plaques and neurofibrillary tangles (NFTs). However, no single-gene-manipulation animal models of AD have so far reproduced robust phenotypes in both. This suggests current modeling approaches may have failed to reach core biological processes underlying AD. Based on several lines of evidence, we hypothesize microglial dysregulation may lie at the core of AD and is a, if not the, common primary factor underlying all major AD pathologies. To test this hypothesis, we generate a mouse model in which multiple mechanisms of microglial cytokine regulation are perturbed. We employ, together with the microglial lineage-targeting cx3cr1-cre, a conditional mutation in ric8a, a gene encoding an essential co-factor for multiple subclasses of Galpha heterotrimeric G proteins, including Gi, Go, and Gq. We find this cell type-specific mutation result in severe dysregulation of microglial cytokine expression in vitro. It affects both basal and activated expression of several cytokines, including TNFalpha and IL-1beta. In vivo, this mutation also results in stepwise elevation in the expression of these cytokines, concomitant with aging. Furthermore, it results in secondary increases in APP and related genes. At the cellular level, we observe strong phenotypes similar to those in AD including both amyloid plaque and NFT-like features. We further observe severe astrogliosis as well as neurodegeneration, including cortical thinning and corpus callosum agenesis. These results strongly suggest a critical primary role of microglial cytokine dysregulation in AD pathogenesis. They provide an unprecedented opportunity for gaining potentially ground-breaking mechanistic insights into the cause of AD.



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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.07

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

Support: AARG-18-533363
NIA R21 AG059223

Title: Chronic inhibition of phospholipase D1 prevents synaptic dysfunction and memory deficits in a mouse model of Alzheimer’s disease

Authors: C. NATARAJAN[1], K. Z. BOURNE[1], B. TUMURBAATAR[1], G. TAGLIALATELA[2], *B. KRISHNAN[3];
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Abstract: **Background:** Phospholipase D (PLD), a lipolytic enzyme that breaks down membrane phospholipids, is also involved in signaling mechanisms downstream of seven transmembrane receptors. Abnormally elevated levels of PLD activity are well-established in Alzheimer’s Disease (AD), implicating the two isoforms of mammalian phosphatidyl choline cleaving PLD (PC-PLD1 and PC-PLD2). Previously, we presented and published our study establishing the synaptic dysfunction and underlying memory deficits. Briefly, we demonstrated using human clinical samples and 3XTg-AD model of AD that PLD1 overexpression contributes to the synaptic changes underlying the neuropathology of AD and related dementia. PLD1 signaling mechanisms include membrane trafficking, cytoskeletal reorganization and autophagy. **Method:** Synaptosomal Western blot analysis on 3XTgAD mice hippocampus [mouse model

with overexpression of human amyloid precursor protein (APP), presenilin1 gene (PSEN1) and microtubuleassociated protein tau (MAPT) causing neuropathology progressing comparable to that in human AD patients] were used to investigate neuronal PLD1 expression and function. Long-term potentiation of PLD1 dependent changes using pharmacological approaches in *ex vivo* slice preparations from wildtype and transgenic mouse models were used to assess synaptic perturbations that were first studied using the novel object recognition memory (NOR) and fear conditioning (FC) paradigms. Chronic PLD1 small molecule inhibitor treatment was assessed in two different age-groups to ascertain the efficacy of treatment at different stages of AD-like memory deficit progression in the animal model. Lastly, brain tissues from these animals were subjected to Western Blot analyses to ascertain the potential signaling mechanism that is perturbed/altered by overexpression of PLD1. **Result:** Aberrant PLD1-driven synaptic mechanisms play a critical role in the memory deficits associated with AD and related dementia. Changes in the protein expression of PLD1-associated pathways were assessed to further understand the mechanism underlying the synaptic perturbation. **Conclusion:** Using well-tolerated small molecule inhibitors for an inducible isoform of a second-messenger system, that is aberrantly recruited post-developmentally, we have conducted a preclinical investigation into a potential pathway amenable to therapeutics that can be used in combination with other approaches in preventing the progression of synaptic dysfunction and underlying memory deficits in AD and related dementia.

Disclosures: C. Natarajan: None. **K.Z. Bourne:** None. **B. Tumurbaatar:** None. **G. Taglialatela:** None. **B. Krishnan:** None.

Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.08

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

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NIH-P20GM113123
ND EPSCoR UND-0021228

Title: Effects of probiotic supplementation on serum and brain short chain fatty acids in the App $^{NL-G-F}$ mouse model of Alzheimer’s disease

Authors: *H. KAUR[1], M. Y. GOLOVKO[1], D. C. DARLAND[2], C. K. COMBS[1];
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Abstract: The intestinal microbiota and its metabolites, particularly short-chain fatty acids (SCFAs), have been implicated in gastrointestinal physiology, immune function, host metabolism, and even in behavior. However, their role in Alzheimer's disease is unclear. This study was performed to investigate whether probiotic administration influences levels of intestinal microbiota and their metabolites in a fashion that may affect brain changes in a mouse model of AD. Wild type (WT) control C57BL/6 mice were compared to a mouse line that has the human Aβ sequence knocked-in to the mouse APP gene along with three disease causing mutations (*App*$^{NL\text{-}G\text{-}F}$). The animals at 6-8 months of age were randomly divided into two groups and orally treated with vehicle or probiotic (VSL#3) for 8 weeks. Fecal microbiome analysis was performed to study the effect of probiotic supplementation on intestinal microbiota. Aβ, GFAP, Iba-1, c-Fos and Ki67 immunohistochemistry were performed on brain sections. Short chain fatty acids (SCFA) were also analyzed in serum and brains using UPLC-MS/MS. The results showed *App*$^{NL\text{-}G\text{-}F}$ mice had distinctly unique fecal microbiome compared to WT mice. VSL#3 supplementation resulted in a dramatic change in microbiota composition in both WT and *App*$^{NL\text{-}G\text{-}F}$ mice. Although *App*$^{NL\text{-}G\text{-}F}$ mice demonstrated the expected increases in Aβ, GFAP, and Iba1 hippocampal immunoreactivity compared to WT mice, there were no obvious differences due to VSL#3 feeding. Analysis of hippocampal Ki67, a marker of neurogenesis, revealed decreased immunoreactivity in *App*$^{NL\text{-}G\text{-}F}$ mice that was also not affected by VSL#3 feeding. However, VSL#3 supplementation resulted in a dramatic increase in hippocampal c-Fos immunostaining, in particularly the *App*$^{NL\text{-}G\text{-}F}$ mice demonstrating a clear effect of diet on their brains. This correlated with significant increases in hippocampal levels of SCFA, lactate and acetate, in the VSL#3 fed *App*$^{NL\text{-}G\text{-}F}$ mice. Interestingly, *App*$^{NL\text{-}G\text{-}F}$ hippocampi had significantly elevated levels of bacterial derived iso-butyrate compared to WT mice, regardless of diet, demonstrating a correlation with their intestinal dysbiosis. These data indicate intestinal dysbiosis exists in the *App*$^{NL\text{-}G\text{-}F}$ mouse model of AD which correlates with elevated levels of SCFA, iso-butyrate, in their brains. The dysbiosis could be manipulated with probiotic supplementation leading to elevated levels of additional SCFA, lactate and acetate, in the *App*$^{NL\text{-}G\text{-}F}$ mouse brains correlating with robust changes in a neuronal marker of activity, c-Fos.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

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Presentation Number: 106.09

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

Support: AG016976
R01 AG43511
Cure Alzheimer's Fund

Title: Phospho-tau in synapses and microglial activation are more proximate correlates to cognition than plaques and tangles

Authors: *A. C. AMARAL, P. RAMANAN, M. S. T. CHONG, A. D. BALDEON, C. AGUERO, C. ROIG-ARSEQUELL, N. SAEZ-CALVERAS, D. A. DENBOW, P. M. DOOLEY, T. GOMEZ-ISLA;
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Abstract: BACKGROUND: It is widely assumed that plaques and tangles are causally related to cognition in Alzheimer's disease (AD). However, data from several studies including our own suggest that relationships between plaques, tangles, and cognition do not suffice to reliably predict clinical outcome on individual basis. Some individuals seem resilient to the presence of plaques and tangles without demonstrating the typical patterns of neuronal and synaptic loss or a decline in cognitive function. Our previous studies suggested that resilient brains exhibit decreased signs of neuroinflammation, including reduced glial cell reaction and a distinct cytokine expression profile when compared to typically demented AD patients. GOAL: To investigate the closest correlates to cognition in a large collection of brains with and without AD pathological changes at postmortem. METHODS: We analyzed brain tissue samples from 104 age-matched participants in the Religious Order Study and Memory and Aging Project (ROSMAP) study at Rush University, including 26 cognitively normal without AD-pathology (Control), 26 cognitively impaired without AD-pathology (Frail), 26 cognitively normal with AD-pathology (Resilient), and 26 cognitively impaired with AD-pathology (AD). All subjects underwent extensive longitudinal cognitive assessments prior to death. Detailed neuropathological quantitative measures of tangles, plaques and reactive astrocytes and microglia were conducted in two regions of interest, Superior Temporal Sulcus and Prefrontal Cortex. Levels of soluble phospho-tau (p-Tau) in synaptoneurosome fractions were measured by Western blot and sensitive ELISA. Studies on additional markers of inflammation are currently ongoing. RESULTS: There was a significant increase of soluble p-Tau in synapses and number of reactive microglia cells (CD68+) in AD compared to Resilient brains. Both measures closely and significantly correlated with antemortem cognitive scores. Interestingly, Frail brains also exhibited a significant increase in the number of activated microglial cells when compared to Control brains, and the burden of reactive microglia was significantly correlated with cognitive measures prior to death. CONCLUSION: In this study microglial activation was found to be the closest correlate to cognition regardless of the presence or absence of classic AD pathology (e.g. plaques and tangles) at postmortem. Differential microglial responses could potentially influence the likelihood of developing cognitive impairment. Modulating brain inflammatory response may help preserve cognitive function in the elderly.

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Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

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Presentation Number: 106.10

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

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P60AA011605
U24AA020024
U54AA019767
T32AA007573
K08AA024829
K01AA025713

Title: Alzheimer's disease markers are increased in postmortem human alcoholic brain and models of binge ethanol *in vivo*

Authors: L. G. COLEMAN, JR[1], R. P. VETRENO[2], L. QIN[3], J. Y. ZOU[4], J. SONG[5], *F. T. CREWS[6];
[2]Sch. of Med., [1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Bowles Ctr. Alcohol Studies, Univ. North Carolina, Sch. Med., Chapel Hill, NC; [4]Univ. North Carolina, Chapel Hill, Chapel Hill, NC; [5]Univ. of North Carolina, Chapel Hill, Chapel Hill, NC; [6]Skipper Bowles Ctr. Alcohol, Chapel Hill, NC

Abstract: Epidemiologic studies find an association between heavy alcohol consumption and the incidence of Alzheimer's disease (AD). Consumption during early life i.e. adolescence or young adulthood may have a greater impact (Mukamal et al 2003, Langballe et al 2015). We investigated whether markers of AD pathology are increased in postmortem human alcoholic brain and whether adolescent intermittent ethanol (AIE) and chronic binge ethanol in the 3xTg mice AD model increase AD markers in adulthood. We also assessed whether ethanol acutely increases expression of AD markers *in vitro.* Expression of $\beta_{(1\text{-}42)}$ amyloid, ptau-181, and GSK3β were measured by Western Blot postmortem human alcoholic cortex Brodmann Area 25 (BA25) and hippocampus from New South Wales Tissue Bank. RT-PCR was used to assess gene expression changes for AD markers APP, MAPT, PSEN1, CDK5, GSK3β, and BACE1 in human alcoholic brain as well as in adult Wistar rats (P95) after AIE (5g/kg, i.g. 2 day on 2 day off, P25-55). Adult 3xTg AD mice (APPSwe, tauP301, $Psen1^{tm1Mpm}$) received 10 days of binge ethanol (5g/kg) during adulthood, and expression of AD markers was measured 24 hours after the last dose of ethanol. In human alcoholic cortex (BA25), increased protein levels of aggregate forming $\beta_{(1\text{-}42)}$ amyloid (1.8-fold), ptau-181 (17%), and GSK3β (2-fold) were found. Gene expression of MAPT, BACE1, CDK5, and GSK3β correlated with the blood alcohol concentration at death. AIE increased gene expression of PSEN1 (2-fold), MAPT (2-fold), and APP (2-fold) in adult hippocampus (P95). Binge ethanol (5g/kg, 10 days) in the 3xTg mouse acutely increased AD gene markers APP (4-fold) and MAPT (5-fold) in frontal cortex as well as in hippocampus (APP 3-fold and MAPT 3.5-fold), and in *ex-vivo* brain slice culture from 3xTg

mice (3-fold APP, 1.9-fold MAPT) suggesting ethanol may accelerate AD pathology in this model. Ethanol also induced expression of APP (1.8-fold), MAPT (1.25-fold) and BACE (2-fold) in SH-SY5Y neuroblastoma cells. Thus, markers of AD pathology are increased in postmortem human alcoholic brain and *in vivo* after binge ethanol. These findings suggests a potential causal link between early life alcohol abuse and risk for of AD pathology later in life.

Disclosures: **L.G. Coleman:** 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.; EMD Serono. **R.P. Vetreno:** None. **L. Qin:** None. **J.Y. Zou:** None. **J. Song:** None. **F.T. Crews:** 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.; EMD Serono.

Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.11

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

Support: P50 AT008661-01 from the NCCIH and the ODS

Title: Inhibition of inflammasome activity and ASC speck formation in response to sterile stress signals in Alzheimer's disease

Authors: M. SEBASTIAN-VALVERDE[1], T. FROLINGER[2], F. HERMAN[1], *G. M. PASINETTI[1];
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Abstract: Psychological stress acts as a risk factor for a number of chronic disorders, including Alzheimer’s disease (AD). Recent studies in our lab and others support the hypothesis that inflammasome complexes, such as the NLRP3, translate sterile or pathogenic danger signals into interleukin 1β (IL-1β) inflammatory responses, exhibit prionoid-like properties, and facilitate amyloid β (Aβ) oligomerization. Our objective is to determine if psychological stress can confer susceptibility to AD phenotypes via activation of inflammasome complexes by sterile inflammatory signaling, such as through high mobility group box-1 (HMBG-1) and ATP, and if so to develop novel therapeutic approaches that target NLRP3 inflammasome activation. Here, we show upregulation of *hmgb-1 ($p<0.001$), IL-1β ($p<0.01$), and nlrp3 ($p<0.05$)* in mice medial prefrontal cortex in a model of chronic unpredictable stress. We further show that mice exposed to this paradigm exhibit cytosolic associated speck-like protein containing a CARD (ASC) speck formation - a readout for inflammasome activation - medial prefrontal cortex microglia

(Pasinetti, Personal Communication). These results in a model of stress-induced depression parallel those observed in both mouse and human AD brains. Using an *in-vitro* model with mCerulean-ASC labeled murine macrophages, we show priming with HMGB-1, followed by ATP stimulation, promotes ASC speck formation. We further carried out a virtual screen to identify select small molecule compounds from a library that target the nucleotide-binding domain of the NLRP3 protein. Activity of this domain is critical for both inflammatory responses and ASC speck formation. Using primary microglia cultures stimulated with LPS+ATP and IL-1ß release as a readout for inflammasome inhibition, we identified fifteen compounds that exhibited IC_{50} values in the low µM range. The three compounds with sub µM IC_{50} values (3.67, 9.24, 11.27 µM) were found to inhibit ASC speck oligerimization in mCerulean-ASC labeled macrophages. Future experiments using a 5 x FAD mouse model will examine if these compounds suppress prionoid activities of the ASC speck and exacerbated AD pathologies by stress.

Disclosures: **M. Sebastian-Valverde:** 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.; P50 AT008661-01 from the NCCIH and the ODS. **T. Frolinger:** None. **F. Herman:** None. **G.M. Pasinetti:** A. Employment/Salary (full or part-time):; James J Peters VA Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; P50 AT008661-01 from the NCCIH and the ODS.

Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 106.12

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

Support: T-Neuro Pharma, Inc. project support
Joseph Drown Foundation grant support
NIH grant 1 R21 NS054162-01

Title: Aberrant resident memory CD8 T cells that elicit Alzheimer's (AD)-like neurodegeneration in mice are elevated in AD patient blood and brain

Authors: *C. J. WHEELER[1], A. PANWAR[2], A. RENTSENDORJ[3], M. JHUN[3], R. CORDNER[4], N. YEAGER[4], L.-W. JIN[5], Y. KORONYO[3], M. KORONYO-HAMAOUI[3], K. L. BLACK[3], D. VAN DAM[6], P. P. DE DEYN[6], V. YAMAMOTO[7], K. A. TRUJILLO[8];
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Sci., [2]Cedars-Sinai Med. Ctr., Los Angeles, CA; [5]Med. Pathology and Lab. Med., Univ. of California, Davis, Davis, CA; [6]Biomed. Sci., Univ. of Antwerp, Antwerp, Belgium; [7]Cancer Biol., Univ. of Southern CA & Brain Mapping Fndn., Los Angeles, CA; [8]T-Neuro Pharma, Inc., Albuquerque, NM

Abstract: There have been over 400 clinical trials for Alzheimer's disease (AD) targeting the Aβ peptide to counteract amyloidosis-mediated neurodegeneration. Amyloidosis, however, may be insufficient to cause neurodegeneration, and this may contribute to the high failure rate in such trials. Indeed, numerous animal models for AD as well as humans can exhibit robust amyloidosis without substantial neurodegeneration, suggesting that a missing factor(s) is required for AD neurodegeneration. Identifying such a factor(s) may promote improved drug trials as well as diagnosis for AD. We hypothesized that such a factor(s) is age-dependent in humans, yet distinct between experimental animals and humans. Homeostatic expansion of CD8 T cells is among the most prominent properties of human aging, but is markedly subdued in experimental animals. We showed that uniform homeostatic expansion of antigen-specific resident-memory CD8 T cells (TRM) induced in nude mice promotes diffuse amyloid plaques in brain, fibrillary inclusions in neurons, neuroinflammation, and cognitive impairment with age, with robust loss of neurons, synaptic markers and brain mass; all key hallmarks of AD neurodegeneration. We used this model to identify gene expression profiles and antigen-specific biomarkers for pathological CD8 TRM in human patients, and found both to be markedly increased in AD brain. In blood, a single resident-memory T cell gene (CD103/ITGAE) exhibited significantly increased expression in AD, and tracked significantly with disease with minimal false-positives (over 40% AD vs. less than 5% controls). In addition, staining of antigen-specific CD8 TRM in AD and MCI blood with peptide HLA reagents was significantly altered relative to controls, with their levels correlating with cognitive decline in MCI patients. Together, this suggests that aberrant CD8 T cell aging and TRM are involved in human AD. Specifically, CD103+ CD8 TRM appear to be significantly expanded in AD blood, with antigen-specific subpopulations changing in proportion to early cognitive decline. This points to the migration of specific pathological T cells from blood into brain, which may represent a potential missing disease factor in AD. Tracking these cells may be useful in diagnosis, and targeting them alone or together with Aβ may represent a novel approach to treating AD neurodegeneration. This work suggest that amyloidosis may not be solely responsible for neurodegeneration in AD, sheds light on potential new approaches to AD diagnosis and treatment, and has important implications for the involvement of adaptive immune cell dysfunction in age related tissue pathology in general.

Disclosures: C.J. Wheeler: A. Employment/Salary (full or part-time):; Chief Scientific Officer, T-Neuro Pharma, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Research program support, T-Neuro Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock ownership, T-Neuro Pharma, Inc., Patent authorship, assigned to Cedars-Sinai Med Ctr.. **A. Panwar:** None. **A. Rentsendorj:** None. **M. Jhun:** None. **R. Cordner:** None. **N. Yeager:** None. **L. Jin:** None. **Y. Koronyo:** None. **M. Koronyo-Hamaoui:** None. **K.L. Black:** None. **D. Van Dam:** None. **P.P. De Deyn:** 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.; Contracted Research collaborator, T-Neuro Pharma, Inc.. **V. Yamamoto:** None. **K.A. Trujillo:** A. Employment/Salary (full or part-time):; Chief Executive Officer, T-Neuro Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock ownership, T-Neuro Pharma, Inc..

Nanosymposium

106. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Room S103

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

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Grant-in Aid for Science Research C, 19K06896 from the Ministry of Education, Culture, Sports, Science and Technology, Japan

Title: Distinct microglial response against Alzheimer's pathologies characterized by P2Y12 receptor

Authors: *N. SAHARA[1], J. MAEDA[1], T. MINAMIHISAMATSU[1], M. SHIMOJO[2], M. ONO[1], K. MINATOHARA[1], H. TAKUWA[1], Y. TAKADO[1], B. JI[1], M.-R. ZHANG[1], M. HIGUCHI[3]; [2]Dept. of Functional Brain Imaging Res., [1]Natl. Inst. of Radiological Sci., Chiba, Japan; [3]Nat Inst. Radiol Sci., Chiba, Japan

Abstract: Microglia is the resident phagocytes of the central nervous system, and its activation is considered to play an important role in the pathology of neurodegenerative diseases. At present, it is still unclear whether microglial activation occurs prior to the formations of senile plaques and neurofibrillary tangles (NFTs) in Alzheimer’s disease. Recent studies with single-cell RNA analysis of CNS cells in neurodegenerative conditions revealed that the transition from homeostatic microglia to disease-associated microglia (DAM) was defined by changes of gene expression levels. The P2Y12 receptor is one of homeostatic microglia markers and strictly down-regulated in neruodegenerative conditions. However, little is known about temporal change of P2Y12 expression during plaque and/or NFT formation. To further evaluate the significance of P2Y12 during neurodegeneration, we have generated anti-P2Y12 antibody and examined P2Y12 expression in proteinopathy mouse models. As results, we observed that both human AD brains and tauopathy mice (rTg4510 and PS19 mouse lines) had decreased P2Y12 receptor levels in brain regions with tau pathology in response to DAM activation. In contrast to P2Y12 reduction, the mitochondrial 18-kDa translocator protein (TSPO) as a neuroinflammation

marker was accumulated in microglia of tauopathy mice. On the other hand, P2Y12 was not decreased during β-amyloid (Aβ) plaque formation in APP mouse models. Most of neuritic plaques in these APP mouse models were surrounded by microglia labeled with Iba1, TSPO, and P2Y12 antibodies whereas plaques in human AD brains were not associated with P2Y12. This data suggests that Aβ plaques in APP mouse models differ from those in human AD brains. Aβ plaques without pathological tau influence may sequester P2Y12-positive microglia in APP mice. Taken together, the homeostatic microglial status was highly sensitive to NFT and plaque formations. In any case, P2Y12 could be a desirable target for preventing proteinopathies.

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Nanosymposium

107. Motor Neuron Disease Mechanisms

Location: Room N426

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 107.01

Topic: C.06. Neuromuscular Diseases

Support: PWB, NIH R01 NS28785
LQ, Graig Neilsen Grant 381793
PWB, Drexel CURE Grant 4100062203

Title: Etiology investigation of hereditary spastic paraplegia-SPG4 by transgenic mouse model and isogenic human induced pluripotent stem cell derived neuronal model

Authors: *L. QIANG, E. PIERMARINI, A. NICEFORO, H. MURALIDHARAN, S. AKARSU, P. YATES, P. W. BAAS;
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Abstract: In order to understand the mechanistic etiology of HSP-*SPG4* (hereditary spastic paraplegia resulting from mutations of *SPAST*), we are using transgenic mice as well as neurons derived from isogenic lines of hiPSC (human induced pluripotent cells). There has been controversy in the field as to whether the disease is caused by toxicity of the mutant spastin proteins or lack of sufficient spastin function. Our hypothesis is that mutant spastin proteins impose toxic effects that give rise to corticospinal die-back, and that insufficient functional spastin heightens the axon's vulnerability to these toxic effects. A transgenic mouse developed in our lab expressing human mutant spastin (C448Y missense mutation) with no reduction in endogenous mouse spastin shows adult-onset gait deficiency and corticospinal die-back, reminiscent of the human disease. We are now expanding these studies to include a mouse with one deleted spastin allele, and we have found that the phenotype of this mouse does not display

these disease characteristics. However, when we crossed the two mice, the double-transgenic showed a more severe degenerative phenotype than either of the two parent mice, thus providing the basis for our hypothesis. To delve deeper into mechanism, we generated isogenic hiPSC lines that either delete one*SPAST*allele or harbor either the C448Y mutation or the S245X truncation mutation. Multiple indicators of axonal degeneration were observed in forebrain glutamatergic neurons differentiated from the lines expressing the mutants, but not from the knockdown line. The neurons from the mutant lines display low but detectable levels of M1, the isoform of spastin that our previous studies suggested is the source of the toxicity when mutated. Elevated activity of HDAC6 (histone deacetylase 6), the chief tubulin deacetylase, in neurons expressing the mutants, but not in neurons with reduced spastin, suggest a potential pathway for the toxicity. Other studies implicate diminished microtubule mobility as the culprit for the greater vulnerability of the axons caused by reduced spastin function. Taken together, these results are a step forward in our efforts to develop an innovative toolbox of targets for therapy, as well as preclinical model systems for testing them.

Disclosures: L. Qiang: None. **E. Piermarini:** None. **A. Niceforo:** None. **H. Muralidharan:** None. **S. Akarsu:** None. **P. Yates:** None. **P.W. Baas:** None.

Nanosymposium

107. Motor Neuron Disease Mechanisms

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Presentation Number: 107.02

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Title: Membralin deficiency dysregulates astrocytic glutamate homeostasis leading to ALS-like impairment

Authors: *L.-L. JIANG, B. ZHU, X. LI, T. HUANG, H. XU;
Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Mechanisms underlying motor neuron degeneration in amyotrophic lateral sclerosis (ALS) are yet unclear. Specific deletion of the ER-component membralin in astrocytes manifested postnatal motor defects and lethality in mice, causing the accumulation of

extracellular glutamate through reducing the glutamate transporter EAAT2. Restoring EAAT2 levels in membralin KO astrocytes limited astrocyte-dependent excitotoxicity in motor neurons. Transcriptomic profiles from mouse astrocytic membralin KO motor cortex indicated significant perturbation in KEGG pathway components related to ALS, including downregulation of *Eaat2* and upregulation of *Tnfrsf1a*. Changes in gene expression with membralin deletion also overlapped with mouse ALS models and reactive astrocytes. Our results shown that activation of TNF receptor (TNFR1)-NFκB pathway known to suppress *Eaat2* transcription was upregulated with membralin deletion. Further, reduced membralin and EAAT2 levels correlated with disease progression in spinal cord from SOD1-mutant mouse models, and reductions in membralin/EAAT2 were observed in human ALS spinal cord. Importantly, overexpression of membralin in $SOD1^{G93A}$ astrocytes decreased TNFR1 levels and increased EAAT2 expression, and improved motor neuron survival. Importantly, upregulation of membralin in $SOD1^{G93A}$ mice significantly prolonged mouse survival. Together, our study provided a mechanism for ALS pathogenesis where membralin limited glutamatergic neurotoxicity, suggesting that modulating membralin had potential in ALS therapy.

Disclosures: **L. Jiang:** None. **B. Zhu:** None. **X. Li:** None. **T. Huang:** None. **H. Xu:** None.

Nanosymposium

107. Motor Neuron Disease Mechanisms

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Presentation Number: 107.03

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R21-NS103118
Robert Packard Center for ALS Research

Title: Amino acid deprivation promotes C9orf72-linked RAN translation via activation of the integrated stress response

Authors: *A. T. NELSON, A. R. HAEUSLER, D. TROTTI;
Neurosci., Thomas Jefferson Univ., Philadelphia, PA

Abstract: The C9orf72 (GGGGCC)n repeat expansion leads to the production of neurotoxic dipeptide repeat proteins (DPRs) by an unconventional mechanism known as repeat-associated non-AUG (RAN) translation. Recently, activation of the integrated stress response (ISR) by a number of different cellular stressors has been shown to increase the occurrence of RAN translation without increasing AUG-driven translation (PMC6365928). The core event in the ISR is phosphorylation of the α subunit of eukaryotic initiation factor 2 (eIF2α), which is carried out by one of three kinases: PERK, PKR, and GCN2, each of which is activated by various cellular stressors (PMC5048378). Stress-induced increases in RAN translation have specifically been

found to be mediated by PERK and PKR (PMC6365928). However, the contribution of GCN2, which is known to be activated by nutritional and metabolic imbalances, remains to be investigated. This is particularly relevant to understanding ALS pathogenic mechanisms because inhibition of the mitochondrial respiratory chain has been observed in ALS (PMC4492815, PMC5834494), which may disrupt amino acid homeostasis and lead to GCN2 activation. To study whether GCN2 plays a role in promoting RAN translation, we cultured human embryonic kidney (HEK) cells in a nutritional medium lacking arginine (amino acid deprivation paradigm) and co-transfected them with two DNA constructs: 1) a RAN-driven construct encoding the GGGGCC repeat expansion with a C-terminal reporter for detection of DPR synthesis, and 2) an AUG-driven construct encoding mIFP, a far-red fluorescent reporter. This allows us to monitor RAN and AUG-driven translation separately and assess their individual responses to the amino acid deprivation paradigm. We show that amino acid deprivation leads to robust depression of AUG-driven translation with concomitant up-regulation/preservation of RAN translation. These studies highlight a decoupling of RAN and AUG-driven translation in response to stress (perhaps due to different 5' cap requirements) and strengthen conclusions in the field about the mechanism and molecular triggers of C9orf72-linked RAN translation.

Disclosures: **A.T. Nelson:** None. **D. Trotti:** None. **A.R. Haeusler:** None.

Nanosymposium

107. Motor Neuron Disease Mechanisms

Location: Room N426

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 107.04

Topic: C.06. Neuromuscular Diseases

Title: Genetic variants and alterations in WWOX lead to tau phosphorylation and mis-localization in post-mortem ALS motor cortex

Authors: ***G. SADRI-VAKILI**[1], T. PETROZZIELLO[1], A. N. MILLS[1], S. M. K. FARHAN[2], S. DUJARDIN[2], A. C. AMARAL[2], T. GOMEZ-ISLA[2], B. T. HYMAN[2], K. VAKILI[3];
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Abstract: Understanding the underlying pathogenic mechanisms capable of altering the course of Amyotrophic Lateral Sclerosis (ALS) are crucial for the development of new therapies. One such candidate is the WW domain-containing oxidoreductase (WWOX) gene whose role in DNA damage response and neurodegeneration is widely reported. We sought to determine whether dysregulation in WWOX may contribute to ALS pathogenesis given that our genetic analysis in 4,366 ALS samples from Project MinE revealed several rare genetic variants in WWOX which were absent in gnomAD. The Short-chain Dehydrogenase/Reductase domain of WWOX, containing the two ALS specific mutations, inhibits GSK3β activation and in turn decreases tau

phosphorylation and accumulation. Therefore, we hypothesized that alterations in WWOX may lead to an increase in GSK3β activity and tau phosphorylation. As predicted there was a significant decrease in WWOX levels in post-mortem ALS motor cortex compared to controls. In order to determine whether GSK3β activity and tau phosphorylation are altered in ALS, we assessed the levels of these proteins in three different cellular fractions in human post-mortem motor cortices (total fraction, cytosolic fraction, and synaptoneurosomes (SNs)). Our results demonstrated that there was a significant increase in phosphorylated GSK3β in ALS SNs compared to controls. Although total tau levels were not changed in ALS, there was a significant increase in tau phosphorylation in the SNs derived from ALS compared to the corresponding cytosolic fractions. In addition, phosphorylated tau levels in the SNs derived from ALS motor cortex were significantly increased compared to controls. Interestingly, there was also a trend towards a decrease in WWOX levels in the SNs in ALS motor cortex, suggesting that dysregulations in WWOX may lead to p-tau accumulation and mis-localization in ALS. Together, these findings provide a potential novel mechanism in ALS involving WWOX/GSK3β/tau signaling.

Disclosures: G. Sadri-Vakili: None. **T. Petrozziello:** None. **A.N. Mills:** None. **S.M.K. Farhan:** None. **S. Dujardin:** None. **A.C. Amaral:** None. **T. Gomez-Isla:** None. **B.T. Hyman:** None. **K. Vakili:** None.

Nanosymposium

107. Motor Neuron Disease Mechanisms

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Presentation Number: 107.05

Topic: C.06. Neuromuscular Diseases

Support: R01NS062055

Title: Aberrant mTOR pathway in G93A SOD1 human astrocytes causes motor neuron toxicity

Authors: *V. GRANATIERO, N. SAYLES, G. MANFREDI;
BMRI, Weill Cornell Med., NEW YORK, NY

Abstract: The mTOR pathway has a significant impact on different and important cell functions, including metabolic regulation, cell proliferation and autophagy. Abnormal increase in the number of astrocytes, known as astrocytes activation, or astrogliosis, has being observed in neurodegenerative disorders, such as of Amyotrophic Lateral Sclerosis (ALS). ALS is the most common motor neurons disease, characterized by loss of both upper and lower motor neurons, resulting in muscle denervation, which leads to paralysis and death. While motor neurons are the most affected cells in ALS, studies on the pathophysiology of the disease have highlighted the importance of non-cell autonomous mechanisms, which implicate other cell types in the central

nervous system, including astrocytes. The therapeutic value of modulating mTOR pathway in neurons is the object of debate, because inhibiting mTOR, using the classical mTOR inhibitor rapamycin has been shown to have both beneficial and detrimental effect in ALS disease models. Here we investigated the involvement of the mTOR pathway in ALS astrocytes, using human-derived astrocytes harboring G93A mutant SOD1 causative of familial ALS. We find a strong activation of mTOR pathway in G93A SOD1 astrocytes, with resulting autophagy inhibition, abnormal cell proliferation and astrogliosis. Furthermore, treating G93A SOD1 mutant astrocytes with the specific mTOR inhibitor torin reverts enhanced cell proliferation, increases autophagy and protects motor neurons from mutant astrocyte-induced cell death.

Disclosures: V. Granatiero: None. **N. Sayles:** None. **G. Manfredi:** None.

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107. Motor Neuron Disease Mechanisms

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Title: Nucleocytoplasmic proteomic analysis uncovers ETF1 and nonsense-mediated decay as modifiers of C9orf72 high repeat expansion toxicity

Authors: *J. ORTEGA[1], E. L. DALEY[1], S. KOUR[2], M. SAMANI[1], L. TELLEZ[1], Y.-H. TSAI[1], T. F. GENDRON[3], C. DONNELLY[2], T. SIDDIQUE[1], J. N. SAVAS[1], U. B. PANDEY[2], E. KISKINIS[1];
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Abstract: The most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is a hexanucleotide (G4G2)n repeat expansion (HRE) in the first intron of the C9ORF72 (C9) gene. The expanded RNA and the dipeptide repeats (DPRs) that are transcribed and translated from the C9-HRE respectively, have been shown to impair nucleocytoplasmic transport. However, the identities of the proteins affected by this defect in mutant C9 motor neurons (MNs), the specific downstream effects of these changes, and their contribution towards neurotoxicity remain unknown. In this study, we have exerted a screening based on a heterologous expression system where we introduced either control (G4G2)8, or

disease (G4G2)58 HRE along with GFP in HEK-293 cells. Using FACS purification and precise biochemical extractions coupled with tandem mass spectrometry, we were able to identified how the nuclear-to-cytoplasmic ratio of the proteome is affected by the C9-HRE. We identified 126 proteins involved in important cellular mechanisms that are disrupted in ALS, such as RNA processing and protein translation, which collectively drive a shift towards a more cytosolic proteome in C9-HRE cells. Amongst these was ETF1, a protein that plays an essential role in directing termination of mRNA translation and it is also a component of the transient SURF complex which recruits UPF1 to stalled ribosomes in the context of nonsense-mediated decay (NMD), a highly conserved degradation pathway of mRNAs that contains nonsense mutations. We validated the higher nuclear levels of ETF1 observed in the proteomic data, in both post-mortem patient tissue and in patient-specific iPSC derived human MNs. Immunolabeling coupled to confocal and SIM imaging analysis also revealed that nuclear ETF1 is mainly localized in nuclear invaginations, in patient iPSC-neurons and postmortem tissue, and mediates a protective shift from protein translation to NMD- dependent mRNA degradation. Overexpression of ETF1 and the NMD-driver UPF1 ameliorate C9-HRE toxicity in vivo. Our findings provide a resource for proteome-wide nucleocytoplasmic alterations across neurodegeneration-associated repeat expansion mutations and highlight ETF1 and NMD as therapeutic targets in C9orf72-associated ALS/FTD.

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Nanosymposium

107. Motor Neuron Disease Mechanisms

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Title: Macromolecular connectivity landscape of mammalian brain identifies novel ALS-relevant complex

Authors: *P. E. A. ASH[1], S. PHANSE[3], R. POURHAGHIGHI[3], F. GOEBELS[3], E. MALOLEPSZA[5], K. TSAFOU[5], A. NATHAN[5], S. CHEN[6], Y. ZHANG[6], S. D. WIERBOWSKI[6], S. BOUDEAU[1], L. Z. M. HU[3], G. CROMAR[4], H. GUO[3], L. A. BECKER[7], A. D. GITLER[7], A. YOUSSEF[8], J. PARKINSON[4], K. LAGE[10,5], H. YU[6], B. L. WOLOZIN[1,2], G. BADER[3], A. EMILI[3,9];
[1]Pharmacol. and Exptl. Therapeut., [2]Neurol., Boston Univ. Sch. of Med., Boston, MA; [3]Donnelly Ctr. for Cell. and Biomolecular Res., [4]Program in Mol. Med., Univ. of Toronto, Toronto, ON, Canada; [5]Broad Inst., MIT, Cambridge, MA; [6]Biol. Statistics and Computat. Biol., Cornell Univ., Ithaca, NY; [7]Dept. of Genet., Stanford Univ. Sch. of Med., Stanfod, CA; [8]Program in Bioinformatics, [9]Ctr. for Network Syst. Biol., Boston Univ., Boston, MA; [10]Dept. of Surgery, Harvard Med. Sch., Boston, MA

Abstract: Connectivity webs mediate the unique biology of the mammalian brain. Yet while cell circuit maps are increasingly available, knowledge of the underlying molecular networks remains limited. Here, we applied multi-dimensional biochemical fractionation with precision mass spectrometry and machine learning to survey endogenous macromolecules in adult mouse brain. We defined a global ‘interactome’ of multi-protein complexes, most never reported before. These brain-selective assemblies have distinct physical and functional attributes and show regional- and cell-type specificity. A striking number are also linked to neurological disorders and disease variants with broad pathophysiological relevance. We identified a putative RNA-binding protein complex associated with amyotrophic lateral sclerosis, which includes Tdp-43, Fus, Tia1 and Atxn2. Through reciprocal pulldowns from murine brain and knockdowns in cultured cells, we validated the interactions and observed an integrated regulatory function in alternative splicing. The fidelity of this RBP complex is responsive to neuronal disease state in a TDP-43$^{WT/WT}$ transgenic mouse model of ALS. Whereas complexed RBPs are co-immunoprecipitated with human TDP-43 from the cortices of transgenic mice, depletion of *Atxn2* confers neuroprotection and reduces the interaction of complexed RBPs with the exogenous TDP-43. By immunofluorescent microscopy, cortical neurons showing cytoplasmic distribution of TDP-43 also showed errant cytoplasmic redistribution of other RBP complex components. Our discovery that ALS-associated RBPs natively assemble as a functional splicing module raises the possibility that a more accurate descriptor of ALS/FTD is as an RBP ‘complexopathy’ that results in part from splicing defects due to insolubility of a subnetwork of RBPs. Thus, this Brain Interaction Map - or BraInMap - resource facilitates mechanistic exploration of the molecular machinery driving core processes and diseases of the central nervous system.

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Nanosymposium

107. Motor Neuron Disease Mechanisms

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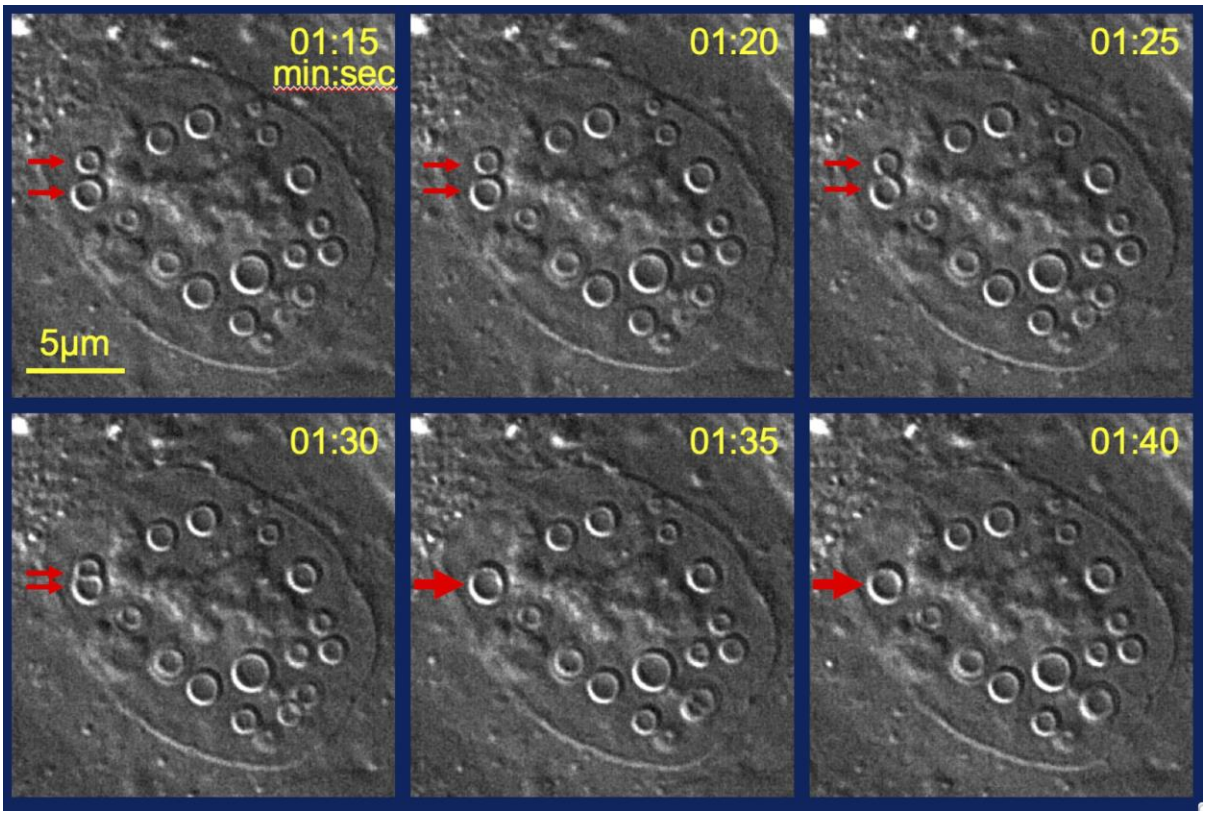
Support: NIH Fellowship 1F32AG059358

Title: Structure and regulation of TDP-43 liquid droplets in the nucleus

Authors: *H. YU, D. W. CLEVELAND;
Ludwig Institute/UCSD, La Jolla, CA

Abstract: Liquid-liquid phase separation (LLPS) drives assembly of membraneless organelles in cells. It is largely unknown if proteins can form ordered structures via LLPS and how these structures are organized under physiological conditions. Here we report the phenomenon of LLPS of TDP-43 into a set of intranuclear, spherical de-mixed droplets. They form a tertiary "liquid-inside-a-liquid" structure, comprised of a close-to-perfect liquid spherical annulus with a higher TDP-43 concentration and an inner liquid spherical core with a lower TDP-43 concentration. While wild type TDP-43 spontaneously de-mixes into intranuclear droplets, intranuclear LLPS is strongly enhanced at physiological conditions by RNA-binding deficient TDP-43. RNA-binding deficient TDP-43 de-mixing produced dynamic spherical shells, as revealed by live imaging and fluorescence recovery after photobleaching. Imaging reveals rapid fusion events in which the outer shells fuse to each other, as do the inner cores. The thickness of the TDP-43 spherical shell was 170±20nm, determined by electron microscopy. Molecules freely exchanged between the de-mixed droplets and the diffuse pool in the nucleus. These liquid droplets remained intact after nuclear envelop disassembly during mitosis and reentered/reassembled in daughter cell nuclei after cell division. Most RNA-binding proteins reported to interact with TDP-43 were not enriched in the droplets, suggesting that RNA mediated this interaction. Chromatin was also excluded from the spherical shell and the inner core. Protein constituents of the de-mixed droplets were determined by biochemical purification and proximity labeling of fixed droplets. Both the oligomerization properties of the N-terminal domain and C-terminal intrinsically disordered region (IDR) were required for the tertiary phase separation. Replacing the IDR of TDP-43 with IDRs of other RNA binding proteins produces phase separated homogenous droplets, not spherical shells. A mutant within the N-terminal domain that disrupts self-oligomerization completely abolished LLPS.



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Nanosymposium

107. Motor Neuron Disease Mechanisms

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Title: C9orf72-related cellular pathology in skeletal myocytes derived from patient-specific induced pluripotent stem cells with amyotrophic lateral sclerosis

Authors: E. LYNCH[1], T. SEMRAD[1], V. BELSITO[1], C. FITZGIBBONS[1], K. HAYAKAWA[3], *M. SUZUKI[1,2];
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Madison, Madison, WI; [3]Lab. of Cell. Biochemistry, Dept. of Animal Resource Sciences/Veterinary Med. Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Amyotrophic lateral sclerosis (ALS) is a late-onset neuromuscular disease with no cure and limited treatment options. Patients experience a gradual paralysis leading to death from respiratory complications on average only 2-5 years after diagnosis. While there is increasing evidence that skeletal muscle is affected early in the disease process, the pathological processes occurring in the skeletal muscle of ALS patients are still mostly unknown. Specifically, the most common genetic cause of ALS, a hexanucleotide repeat expansion in the C9orf72 gene, has yet to be fully characterized in the context of skeletal muscle. In this study, we used the protocol previously developed in our lab to differentiate skeletal myocytes from induced pluripotent stem cells (iPSCs) of *C9ORF72* ALS (C9-ALS) patients in order to create an *in vitro* disease model of C9-ALS skeletal muscle pathology. Of the three *C9ORF72* mutation hallmarks, we did not see any evidence of haploinsufficiency, but we did detect RNA foci and dipeptide repeat (DPR) proteins. Additional abnormalities included changes in the expression of mitochondrial genes and a susceptibility to oxidative stress, indicating that mitochondrial dysfunction may be a critical feature of C9-ALS skeletal muscle pathology. Further, the C9-ALS myocytes had increased expression and aggregation of TDP-43. These data show that skeletal muscle cells experience pathological changes due to the *C9ORF72* mutation. As the next step, RNA sequencing was used to compare C9-ALS myocytes with cells from other ALS backgrounds (sporadic and familial with *TARDBP* or *SOD1* mutation) and found that skeletal myocytes from all ALS lines were down-regulated in four specific genes: *HNRNPK*, *GPC3*, *DCX*, and *BET1L*. Notably, gene ontology analysis revealed that these four genes are involved in vesicle transport, suggesting a common mechanism. Our *in vitro* model could facilitate further study of these pathological mechanisms in ALS skeletal muscle. We are also working on co-culture models to examine how ALS skeletal muscle dysfunction may influence motor neuron viability. Together, we hope that these studies will provide new therapeutic targets against this devastating disease.

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Nanosymposium

107. Motor Neuron Disease Mechanisms

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Support: S31201, RO1

Title: Extracellular vesicles produced by neurons are associated with toxicity spreading in amyotrophic lateral sclerosis and fronto-temporal dementia

Authors: *M. CICARDI[1], B. K. JENSEN[2], K. KRISHNAMURTHY[3], T. R. WESTERGARD[1], D. TROTTI[4];
[2]Jefferson Weinberg ALS Center, Vickie and Jack Farber Inst. for Neurosci., [3]Neurosci., [1]Thomas Jefferson Univ., Philadelphia, PA; [4]Neurosci., Dept. of Neurosci., Philadelphia, PA

Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two devasting and incurable diseases that affect different areas of the central nervous system. In both ALS and FTD neural death firstly occurs in few neurons in a localized area but eventually spreads across the whole central nervous systems (CNS) leading patients to death. The driving force and the biological mechanisms at the basis of the spreading of the diseases are still largely unknown but pivotal to bring ALS and FTD to a halt. The aberrant G_4C_2 repetition in the *C9orf72* gene is the most common genetic cause of both ALS and FTD. The repeat associated non AUG translation (RAN-T) of the G_4C_2 repetitions leads to the production of five different di-peptides proteins (DPRs; polyGA, polyGP, polyGR, polyPA, polyPR), that are linked to various toxic mechanism inside cells. In order to preserve the proteostasis cells try to remove harmful materials from their environment and one route is the production of extracellular vesicles (EVs). EVs are actively released by neurons and their composition is highly dependent on cell pathological status. In this work we extracted extracellular vesicles from NSC34 medium after transfecting the five different DPRs. EVs were extracted by ultracentrifugation collecting a pellet at 21,000xg and a pellet at 100,000xg. Both the EVs populations, analysed by nano-track analysis and western blot, were positive for DPRs. We also observed a difference in the amount of DPRs loaded into the EVs: polyGA, polyPA and polyPR were more abundant than polyGP and polyPR, meaning that the recruitment of DPRs into EVs is differently regulated. Moreover, we studied EVs ability to seed toxicity by mean of a transwell system used to put NSC34 transfected with DPRs in contact with rat primary cortical neurons (CNs) transfected with synaptin-driven Td-Tomato (Td); we followed Td^+ neurons over time and the obtained results suggested that $polyGR^+$ NSC34 were able to seed toxicity in CNs overtime in a larger extent compare to the other DPRs. Secondly, EVs were extracted by medium from NSC34 transfected with the five different DPRs and then added directly onto Td^+ CNs, to evaluate if polyGR toxicity was delivered by EVs. We observed decreased cell viability after exposure to $polyGR^+$ EVs, enforcing the hypothesis that EVs are actual carriers of toxicity. The collected data pointed out that affected neurons continuously produce EVs loaded with DPRs that are then incorporated into still healthy cells, accelerating the degenerative process. Deeper understanding of EVs involvement and role could open the possibility to find new therapeutic targets to halt the progression of ALS and FTD.

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Nanosymposium

107. Motor Neuron Disease Mechanisms

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Title: Examining mutation-specific impact on the long, distal motor axon in ALS using iPSC-derived motor neurons

Authors: *K. L. MARSHALL, L. RAJBHANDARI, A. TAGA, A. VENKATESAN, N. J. MARAGAKIS, M. H. FARAH;
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Abstract: Distal axon degeneration, dying-back, is a hallmark of motor neuron diseases that precedes symptom onset and motor neuron death both in human patients and animal models. There is no generally accepted explanation for the selective vulnerability of motor neurons in diseases such as Amyotrophic Lateral Sclerosis (ALS). The longest axons tend to be the most susceptible to degeneration; therefore, the pathobiology of the long, distal motor axon in motor neuron disease is an area that must be explored thoroughly in order to understand ALS pathology and discover potential novel interventions for patients. While motor neurons derived from human iPSCs (hMNs) hold promise for advancing ALS research, the length of axons, regenerative capacity, and mutant-specific innervation of neuromuscular junctions (NMJs) by these human neurons is not well-characterized. hMNs cluster into circular groups as they grow, and extend axons to other clusters, confounding quantification of axon outgrowth from individual hMNs. To address this, we have cultured hMNs from ALS patients and controls in custom microfluidic devices, and sequestered neuronal cell bodies in the main compartment that extended processes through microgrooves into two adjacent axonal compartments. We determined that devices with ample room in the axonal compartments are appropriate for examining axonal outgrowth, and allow for individual tracing of axons that are millimeters in length. We are able to sever axons at the entry point to the axonal compartments, and observe regeneration. This system lays the groundwork for introducing relevant cell types and gathering electrophysiological data from myocytes innervated by hMNs. We are now exploring the introduction of relevant cell types, such as myelinating Schwann cells and myocytes, into the axonal compartment in order to study ALS mutation-specific effects on structural and functional innervation of NMJs.

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Nanosymposium

108. Dynamic Signal Integration Across Saccades

Location: Room S505

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 108.01

Topic: D.08. Visual Sensory-motor Processing

Title: External inputs and intrinsic dynamics of the superior colliculus revealed by local field potentials

Authors: *C. MASSOT;
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Abstract: The superior colliculus (SC) is a central hub for saccade generation. It receives inputs from multiple visual areas and generates a motor-like activity that is sent to downstream oculomotor structures in the brainstem. Hence within SC, a sensory-to-motor transformation is realized that remains to be understood. To address this gap in knowledge, here we analyzed how SC activity is generated during the production of saccades by dissociating intrinsic activity from activity due to external inputs. To address this question, we used laminar recordings to analyze local field potentials (LFP) and current-source density analysis (CSD) across SC layers. We recorded spikes and LFPs from a 16-channel laminar probe in the SC of two rhesus monkeys performing randomly interleaved delayed, visually-guided and memory-guided saccades. The electrode penetration was orthogonal to the surface of SC and saccade vectors were comparable across all recording contacts. Each session was depth-aligned using a reference channel obtained by CSD analysis. We measured the relationship between spiking activity and LFP using spike-field coherence across depth during different epochs. We also computed a grand-averaged CSD (gCSD) to identify significant sink and sources of electrical current across sessions. We found the following: (1) During the visual epoch, spike-field analysis showed a large coherence and gCSD analysis showed a large sink of currents for dorsal channels; this reflects visual inputs to SC during the presentation of the visual target. (2) During the pre-saccadic epoch, spike-field analysis revealed a marked decrease of coherence compared to the visual epoch and gCSD showed a lack of significant sink and source of currents despite the increase of spiking activity; these are signature of intrinsic dynamics resulting in the averaging out of the current flow. (3) During the production of the saccade, spike-field coherence remained minimum despite the burst of spiking activity; gCSD showed a significant source of current paired with a smaller sink in the middle of the intermediate layers; the peak of spiking activity and of positive LFP appeared to be temporally correlated; this may reflect a strong inhibitory external input to SC. To summarize, SC spiking activity and LFP appear to contain different but complementary information revealing characteristics of SC activity for realizing the sensorimotor transformation for saccade generation.

Disclosures: C. Massot: None.

Nanosymposium

108. Dynamic Signal Integration Across Saccades

Location: Room S505

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 108.02

Topic: D.08. Visual Sensory-motor Processing

Support: NSF Grant 1811543
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NIH Grant EY014800
Research to Prevent Blindness Inc., New York, NY

Title: Understanding the dynamic neural code of extrastriate areas underlying visuospatial integration across saccadic eye movements

Authors: *N. NATEGH[1,2], A. AKBARIAN[1], K. L. CLARK[2], K. NIKNAM[1], B. NOUDOOST[2], Y. ZAMANI[1];
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Abstract: We redirect our gaze using ballistic eye movements, called saccades, thousands of times each day to collect information about the visual world around us. During eye movements, the brain must suppress the induced motion in the visual image projected onto the retina. Filling in these perceptual gaps via integrating the spatial information between the pre- and post-saccadic visual scenes seems critical for providing continuity of visual perception across saccades. We focus on the perisaccadic responses in extrastriate visual areas, which have the requisite visual selectivity to underlie perceptual changes around the time of saccades. To understand the extrastriate neural representation of spatial information across a saccade, we use a combined experimental and computational approach, which enables us to understand the encoding and decoding of visual information at each timepoint relative to the time of a saccade. Using temporally and spatially precise visual probes presented pseudorandomly, we can capture the perisaccadic response modulations of neurons in the middle temporal and V4 areas of macaque monkeys. To understand how the visual information across a saccade is represented in these complex responses, we develop a novel extension of the generalized linear model (GLM) framework, termed the sparse-variable GLM, which enables us to capture perisaccadic changes in neurons' visual responses on a millisecond timescale, and characterize the temporal evolution of the spatiotemporal stimulus kernels underpinning those changes. We describe these time-varying kernels using a set of temporally precise basis functions defined across the neuron's response latency and the time relative to the saccade for each probe location. This description provides a low dimensional representation of the neuron's time-varying spatiotemporal sensitivity using sparse perisaccadic data. In order to understand how perisaccadic sensitivity in extrastriate areas accounts for the integration of pre- and post-saccadic scenes, we use a readout of the model to identify which basis function elements across time and space are relevant to the integration of spatial information across a saccade. Manipulating the gain of this subset of basis elements and studying their impacts on the readout of the perisaccadic visual information, enables us to link multiple neuronal response components to their behavioral counterparts.

Employing this approach we are able to establish how perisaccadic activity in visual extrastriate areas accounts for perisaccadic perceptual phenomena.

Disclosures: **N. Nategh:** None. **A. Akbarian:** None. **K. Niknam:** None. **Y. Zamani:** None. **K.L. Clark:** None. **B. Noudoost:** None.

Nanosymposium

108. Dynamic Signal Integration Across Saccades

Location: Room S505

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 108.03

Topic: E.01. Eye Movements

Support: Canadian Institutes of Health Research (CIHR)
Deutsche Forschungsgemeinschaft (IRTG-1901 and CRC/TRR-135)
Canada First Research Excellence Fund (CFREF)

Title: Predictive influence of static landmarks on visual and memory responses of frontal eye field (FEF) and supplementary eye field (SEF)

Authors: *A. SCHUETZ[1,2], V. BHARMAURIA[3], X. YAN[3], H. WANG[3], F. BREMMER[1,2], J. CRAWFORD[3];
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Abstract: Our environment is filled with visual landmarks that may sometimes indicate the expected location of a future gaze target. Here, we hypothesized that visual responses of neurons in the frontal and supplementary eye fields, FEF, and SEF, i.e. two key areas of the primate gaze control system, may play a key role in integrating allocentric and egocentric information for predictive saccade generation. To test this, we analyzed the visual responses of 102 FEF and 29 SEF neurons recorded during a memory delay saccade task, where rhesus macaques first viewed a large cross-shaped landmark (L) while fixating, followed by a briefly flashed (100 ms) quasi-predictable target (T), located 11° from the cross-center in one of the four oblique directions. After presentation of a mask and a delay period, the monkey had to saccade to the remembered T location (producing motor responses not analyzed here). To map the receptive field of each neuron, the L, fixation point, and T position were varied across trials. From previous findings, we assumed a default visual code of the target in retinal coordinates (Te). To determine the influence of the landmark on the neuronal code and its evolution over time we computed time-resolved intermediate reference frames from Te to allocentric codes (Le, landmark relative to eye; and TLe, target relative to landmark in eye coordinates). In both areas, the Te-Le continuum showed no detectable preference. However, the Te-TLe continuum displayed a preference for

TLe coding from 100 ms after L-onset persisting until 80 ms (time of the VR onset) after T-onset. Then, from the VR onset, the coding preference briefly displayed a bimodal distribution around TLe, suggesting predictive activity related to possible T positions around L. To test this hypothesis, we fit these responses along the Te-Ge continuum (future gaze in eye coordinates). Remarkably, we found a strong Ge preference from 100 ms after L-onset in FEF (but not SEF), with an optimum midway between Te and Ge for FEF (1/3 toward Ge in SEF) coinciding with the bimodal Te-TLe distribution. These results suggest that in the presence of visual landmarks (i) visual space is encoded simultaneously in various reference frames at the single cell and at the population level that (ii) these landmarks allow the brain to create a probabilistic model for the future gaze goal, although distinctly in FEF and SEF.

Disclosures: **A. Schuetz:** None. **V. Bharmauria:** None. **X. Yan:** None. **F. Bremmer:** None. **J. Crawford:** None. **H. Wang:** None.

Nanosymposium

108. Dynamic Signal Integration Across Saccades

Location: Room S505

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 108.04

Topic: E.01. Eye Movements

Support: CIHR
NSERC

Title: Spatiotemporal evolution of egocentric/allocentric multiplexing in frontal eye field (FEF) and supplementary eye field (SEF) neurons following visual landmark shifts in rhesus macaques

Authors: *V. BHARMAURIA[1], A. SAJAD[2], H. ARORA[1], X. YAN[1], H. WANG[1], J. D. CRAWFORD[1];
[1]York Univ., Toronto, ON, Canada; [2]Psychological Sci., Vanderbilt Univ., Nashville, TN

Abstract: Behavioral studies in humans have shown that the visual system optimally combines egocentric (ego) and allocentric (allo) cues for goal-directed movements, but the underlying neural mechanisms are unknown. Based on our recent fMRI results, we focused on two important saccade-related areas in monkey: the frontal eye field (FEF) and supplementary eye field (SEF), which possess visual (V), delay (D), and motor (M) signals for the gaze output command. In ego-only studies, we found that the FEF visual burst (80-180 ms sampling window from target on) coded target relative to eye (Te), whereas the motor burst (- 50-50 ms relative to gaze onset) coded future gaze relative to eye (Ge). First, in these sampling windows, we tested the V and M response fields (RFs) of 147 FEF and 69 SEF neurons (most of them simultaneously recorded from FEF and SEF) in two monkeys which were trained to make gaze shifts in a cue-conflict memory task: a target (T) was flashed (100 ms) in presence of a large

cross shaped landmark (L), and after presentation of a mask and a variable memory delay, the monkey had to saccade to the remember target (T', virtually shifted) in presence of the shifted landmark (L'). We used a model-fitting algorithm to track RF changes along two spatial continua: Te-Ge (ego, to quantify gaze influence) and Te-T'e (allo, to quantify landmark influence). In both areas, along the Te-Ge continuum, the visual response (VR) best fit the T, and motor response (MR) significantly shifted toward G. Along the Te-T'e continuum, the VR best fit the T, and the MR significantly shifted 1/3 toward T' like behavior. To track the timing of this shift, we pooled V, M and visuomotor (VM) neurons in FEF and SEF and time-normalized the neural activity from VR onset until the gaze onset. In both areas, initial V and D responses predominantly encoded Te, but after the mask-off/L'-on, we observed a gradual coding shift toward T'e that was significantly embedded in both areas just before the gaze was imminent (although it was embedded significantly earlier in FEF than SEF). This allo shift along the Te-T'e continuum was coded as a function of the ego code (from Te-Ge) in VM and motor only neurons. Overall, these results show that the cortical motor output is influenced by allo visual cues and multiplexes this influence within ego codes while weighing them gradually during the memory delay.

Disclosures: V. Bharmauria: None. **A. Sajad:** None. **H. Arora:** None. **X. Yan:** None. **H. Wang:** None. **J.D. Crawford:** None.

Nanosymposium

108. Dynamic Signal Integration Across Saccades

Location: Room S505

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Presentation Number: 108.05

Topic: E.01. Eye Movements

Support: NSERC Brain-in-Action CREATE Program
NSERC Discovery Grant
Canada Research Chair Program
OGS: QEII GSST

Title: Cortical networks for transsaccadic updating of grasp orientation: A neuroimaging / functional connectivity study

Authors: *B. BALTARETU[1], S. MONACO[2], J. VELJI-IBRAHIM[1], G. N. LUABEYA[1], J. D. CRAWFORD[1];
[1]York Univ., Toronto, ON, Canada; [2]Univ. of Trento, Ctr. for Mind/Brain Sci., Trento, Italy

Abstract: Coordinated reach-to-grasp movements are often accompanied by rapid eye movements (saccades) that displace the desired object image relative to the retina. Parietal cortex compensates for this by updating reach goals relative to current gaze direction, but its role in the

integration of oculomotor and visual orientation signals for updating *grasp* plans is unknown. Based on a recent perceptual experiment, we hypothesized that inferior parietal cortex (specifically supramarginal gyrus; SMG) integrates saccade and visual signals to update grasp plans in more superior parietal areas. To test this hypothesis, we employed a functional magnetic resonance adaptation paradigm, where an oblong 3D object was first presented at one of two possible orientations (0° or 135°), and then was re-presented at the same orientation (Repeat condition) or at the other orientation (Novel condition). Participants (n=17) fixated on one of two LEDs (on either side of the central grasp object) initially and either fixated the same LED (Fixation condition) upon re-presentation of the object or made a saccade to the other LED (Saccade condition). Participants were then required to grasp the object. In order to determine the functional connections in the brain during the preparation of the grasp (i.e., during object re-presentation), we performed a psychophysiological interaction analysis with right SMG as the hub, whereby we investigated activity in cortical regions related to saccades as compared with fixations. Overall, we found that right SMG and several parietal grasp areas, namely left anterior intraparietal sulcus (aIPS) and bilateral superior parietal lobe (SPL), met our criteria for transsaccadic orientation integration: during movement preparation, they showed task-dependent saccade modulations and, during grasp execution, they were specifically sensitive to changes in object orientation that followed saccades. Finally, SMG showed enhanced functional connectivity with both prefrontal saccade areas (consistent with oculomotor input) and aIPS / SPL (consistent with sensorimotor output). These results support the general role of parietal cortex for the integration of visuospatial perturbations, and provide specific cortical modules for the integration of oculomotor and visual signals for grasp updating.

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Nanosymposium

108. Dynamic Signal Integration Across Saccades

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Presentation Number: 108.06

Topic: D.08. Visual Sensory-motor Processing

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Title: Working memory enhances the synaptic efficacy of visual inputs to prefrontal cortex

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Abstract: A number of psychophysical and neurophysiological studies suggest common neural mechanisms of attention and working memory. Yet, evidence of those commonalities at the neural circuit level is largely absent. We looked for such evidence in a visuomotor circuit of the primate brain where neurons are modulated both by spatial attention and spatial working memory, specifically within visual cortex (area V4) and prefrontal cortex (frontal eye field, FEF). Recent studies show that attention enhances the synaptic efficacy of visual inputs corresponding to attended stimuli. We hypothesized that working memory might likewise enhance inputs corresponding to remembered locations. To test this, we measured the effects of spatial working memory on the efficacy of spikes evoked within the FEF from retinotopically corresponding sites within area V4 of behaving monkeys. After locating sites within the FEF and V4 with overlapping response fields, we recorded the activity of FEF neurons and identified neurons orthodromically activated by electrical stimulation of V4. Rhesus monkeys (macacca mulatta) performed a spatial working memory task: the monkey fixates and a peripheral visual target is presented. The monkey must remember the target location after its disappearance (memory period) and move his eyes to the remembered location to receive a reward after the fixation point disappears at the end of the memory period. Electrical stimulation of V4 occurred during the fixation, target, memory or eye movement periods of the trial. We identified 96 orthodromically activated FEF neurons among a total of 313 neurons recorded in two monkeys. We found that during the memory period, spikes from orthodromically activated FEF neurons were more readily evoked while monkeys remembered locations within the joint response fields than while they remembered other locations. In addition, evoked spikes had shorter latencies while monkeys remembered locations within the joint response fields, and the probability of simultaneous spiking between pairs of FEF neurons was elevated, compared to while monkeys remembered other locations. These results demonstrate that, like attention, working memory enhances the synaptic efficacy of visual inputs at spatially corresponding locations.

Disclosures: B. Noudoost: None. **T. Moore:** None.

Nanosymposium

108. Dynamic Signal Integration Across Saccades

Location: Room S505

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 108.07

Topic: E.01. Eye Movements

Title: Saccade adaptation selectively transfers to spot pursuit

Authors: *S. N. J. WATAMANIUK[1,2], J. B. BADLER[2], S. J. HEINEN[2];
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Abstract: Pursuit of spot targets requires attention, but pursuit of large targets does not. Additionally, catch-up saccades are more prevalent during spot than large-target pursuit and yet there is no difference in steady-state pursuit gain. Therefore, it is possible that catch-up saccades are the attentive element rather than pursuit per se. Alternatively, pre-saccadic signals from the attentive saccadic system may be combined with pursuit signals conferring attentive properties to spot pursuit. Here we test whether the saccadic system contributes to the pursuit drive by adapting the saccadic system, and immediately testing pursuit to determine if adaptation effects appear in the pursuit response. To adapt the saccadic system, observers fixated a central spot and generated saccades to a flashed 3° eccentric target. While the saccade was in progress, the target was displaced 1° toward or away from the fixation point. An EyeLink 1000 recorded eye movements at 1000 Hz and provided gaze contingent target displacement. Saccade adaptation proceeded for 100 trials, following which saccade amplitude was decreased for inward displacements, and increased for outward ones. Following adaptation, observers pursued either a small spot stimulus (.2 deg), a large concentric ring of 8 spots (6° diameter; dot diameter .2 deg), or a 6° diameter ring. All pursuit stimuli moved from the center of the screen either leftward or rightward at a constant velocity of 10°/sec. We found that steady-state eye velocity in the adapted saccade direction was consistently reduced for spot pursuit following inward saccade adaptation. Outward saccade adaptation increased steady-state eye velocity in the adapted saccade direction. With the large stimuli, pursuit adaptation occasionally occurred, but it was inconsistent across observers, and less frequent for the solid ring than the 8-dot ring. The results provide evidence that saccadic adaptation transfers to spot stimuli, and suggest that pre-saccadic signals contribute to smooth eye velocity during pursuit of a small spot. However, these signals are sometimes introduced into large-stimulus pursuit, possibly depending upon the degree to which they activate the saccadic system.

Disclosures: S.N.J. Watamaniuk: None. **J.B. Badler:** None. **S.J. Heinen:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.01

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant AA024757

Title: GDNF overexpression in the VTA prevents relapse of heavy alcohol use and restores mesolimbic dopamine function in rhesus macaques

Authors: *M. M. FORD[1], K. M. HOLLERAN[2], B. GEORGE[2], P. HADACZEK[3], L. E. VANDERHOOFT[1], J. BRINGAS[3], J. NAIDOO[3], J. J. SCHOEN[1], J. L. MCBRIDE[1], J. R. FORSAYETH[3], S. R. JONES[2], K. A. GRANT[1], K. S. BANKIEWICZ[3];
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Abstract: FDA-approved medications are often insufficient in sustaining long-term abstinence in treatment-seeking alcoholics. This stark reality is made clear by the fact that upwards of 90% of alcoholics relapse at least once over a 4-year period following treatment onset. The purpose of the current work was to establish a new gene therapy paradigm for the treatment of alcohol use disorder that reverses deficits in reward pathway function and is long-lasting. Preclinical rodent studies indicate that glial-derived neurotrophic factor (GDNF) is a potent negative regulator of alcohol intake. Hence, we explored the overexpression of GDNF within the VTA as our treatment strategy. Male rhesus macaques were induced to consume alcohol and then provided open access to 4% w/v alcohol and water for a period of 6 months. After a one month forced abstinence period, animals were treated with either AAV2-GDNF or vehicle intra-VTA via MRI-guided infusion (n=4/group; 30 uL/side; 1.0E+13 vector genomes), and then underwent an additional 2 months of abstinence for surgical recovery, viral transduction and stabilization of GDNF expression. Alcohol was then freely available for 6 one-month relapse periods, each separated by a 1-month period of forced abstinence. Vehicle-treated animals increased alcohol consumption by up to 40% on the first day of each relapse, and thereafter returned to their pre-abstinence baseline consumption. In contrast, this initial escalation was prevented in AAV2-GDNF treated animals, and daily consumption was further reduced by 80-90% versus pre-surgical baseline amounts. Post-mortem analysis confirmed GDNF overexpression in the brains of all AAV2-GDNF-treated animals, especially within the ventral striatum. Additionally, this overexpression was associated with robust increases in striatal dopamine turnover, as indicated by increases in the DA metabolites DOPAC and HVA. Ex vivo voltammetry in the nucleus accumbens revealed alterations in both basal tonic and phasic dopamine dynamics as well as putative reversal of previously published ethanol-induced aberrant terminal receptor alterations in the GDNF treated animals compared to vehicle treated animals. Together, these findings suggest that AAV2-GDNF treatment attenuates alcohol consumption and reverses chronic alcohol-induced dopamine system dysregulation. GDNF gene therapy exhibits promising therapeutic potential in preventing relapse, and future work will aim to optimize benefits while minimizing observed adverse effects, such as transient sensorimotor deficits.

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Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.02

Topic: G.08. Drugs of Abuse and Addiction

Title: A potential DNA epigenetic basis for individual differences in susceptibility to alcohol use disorder

Authors: *G. J. KAPLAN, J. CHITAMAN, N. WADDELL, H. XU, R. L. HEDINGER, J. FENG;
Florida State Univ., Tallahassee, FL

Abstract: Nearly 75% of American adults consume some alcohol each year, yet only 7-12% of alcohol drinkers meet clinical criteria for alcohol use disorder (AUD). Elucidating the neural mechanisms underlying susceptibility to uncontrolled drinking may therefore relieve a significant portion of the alcohol disease burden. Epigenetic mechanisms, including DNA methylation, are increasingly implicated in addiction-like behaviors. The recent discovery of DNA methylcytosine dioxygenases (TETs) in the mammalian brain demonstrates the additional layers of DNA epigenetic mechanisms. To date, the functional role of TETs in AUD-like behaviors has yet to be explored. Here, we examined *Tet* (*Tet1, Tet2, Tet3*) expression in the nucleus accumbens (NAc) of mice exhibiting variable sensitivity to developing alcohol behavioral sensitization (ABS) - a form of behavioral plasticity thought to underlie the transition from controlled to uncontrolled drinking. Adult mice were given alcohol (15% w/v, 2.4 g/kg) or saline intraperitoneally for 21 days and assessed for ABS on days 1, 7, 14 and 21. Mice were classified as high or low responders based on locomotor activity scores on day 21. Mice were sacrificed 24 hours after the final test date, and bilateral 14-gauge NAc punches were collected. Analysis with qPCR revealed significant differential expression of *Tet* mRNAs in the NAc between high and low responders, relative to control. Viral-mediated knockdown of *Tet3* in the NAc decreased the magnitude of ABS relative to control, implying a potential DNA epigenetic role for TETs in the development of ABS. Given the broad regulatory function of TETs in gene transcription, we are currently using RNAseq to characterize the transcriptome of ABS high and low responders. These data may provide a ‘snapshot’ of gene expression profiles in the NAc with relevance to AUD.
Key words: alcohol use disorder; DNA methylation; epigenetics; individual differences; nucleus accumbens

Disclosures: G.J. Kaplan: None. **J. Chitaman:** None. **N. Waddell:** None. **H. Xu:** None. **R.L. Hedinger:** None. **J. Feng:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

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Presentation Number: 109.03

Topic: G.08. Drugs of Abuse and Addiction

Support: CIHR Grant PJT 159586
Vanier Canada Graduate Scholarship via NSERC awarded to RH

Title: Prenatal delta 9 tetrahydrocannabinol exposure elicits divergent age and sex dependent cognitive impairments and dysregulation of prelimbic neural activity via disruption of hippocampal molecular signaling cascades and fatty acid synthesis

Authors: *R. M. HUDSON[1], S. FRIER[1], T. D. JUNG[2], W. J. RUSHLOW[3], S. R. LAVIOLETTE[1];
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Abstract: The mammalian hippocampus is a chief neural region involved in cognition and memory formation, and a principal structure mediating the neuropsychiatric side effects of cannabinoid exposure. Despite evidence that cannabis use during pregnancy can precipitate enduring neurocognitive impairments in progeny, epidemiological reports suggest that ~20% of North American pregnant women use cannabis to combat physical and emotional ailments. Evidence suggests that adverse outcomes in offspring, including persistent attentional dysregulation, mnemonic and reward-related processing deficits, and increased neuropsychiatric risk are sexually divergent and attributable to delta-9-tetrahydrocannabinol (THC), the primary psychotropic agent in cannabis. Although hippocampal dysfunction has been previously implicated in these deficits, the contributions of precise neurocircuitry and neurobiological mechanisms to contrasting age- and sex-related neuropsychiatric impairments remain unknown. Given that the ventral hippocampus (VHipp) and prelimbic medial prefrontal cortex (mPFC) facilitate attention, affective processing and memory formation, we explored the hypothesis that prenatal THC exposure dysregulates mPFC neural activity to elicit persistent cognitive deficits via modulation of VHipp molecular signaling cascades. Prenatal THC-exposed male and female progeny of pregnant Wistar rats (3 mg/kg/day, i.p.; gestational day 6 to birth) were employed in experiments combining behavioural pharmacology, molecular assays, and in-vivo extracellular electrophysiology at postnatal day (PND) 21 and 6 months. Male offspring demonstrated increased expression of Peroxisome Proliferator-Activated Receptor (PPAR) subtypes, and markedly reduced mitogen-activated protein kinases (MAPKs), P70S6k, and GSK3 phosphorylation at PND 21 that persist into adulthood, while female offspring showed minimal changes in protein expression regardless of age. Similar age- and sex-dependent disturbances in sociability, anxiety, emotional processing, and mPFC neural activity profiles emerged in prenatal THC-exposed progeny. Our findings implicate the VHipp Akt-GSK3 and MAPK intracellular signaling pathways, and PPAR nuclear receptor systems as critical intracellular targets whereby prenatal THC engenders persistent deficits in attention and memory processing, and cortical desynchronization. These results indicate particularly increased vulnerability of prenatal THC

exposure in male offspring, and suggest important implications for aroused predisposition for psychiatric disorders, including schizophrenia and substance dependence.

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Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.04

Topic: G.08. Drugs of Abuse and Addiction

Support: PIP, Grant/ Award Number: 9671/14

Title: Interoceptive enhancement in early onset consumption to smoked cocaine

Authors: *L. A. DE LA FUENTE DE LA TORRE[1,2], L. SEDEÑO[2], S. SCHURMANN VIGNAGA[2], S. SONZOGNI[3], C. ELLMANN[2], A. GARCÍA[2], M. CETKOVICH[2], E. T. CÁNEPA[3], T. TORRALVA[2], E. TAGLIAZUCCHI[1], A. IBÁÑEZ[2];
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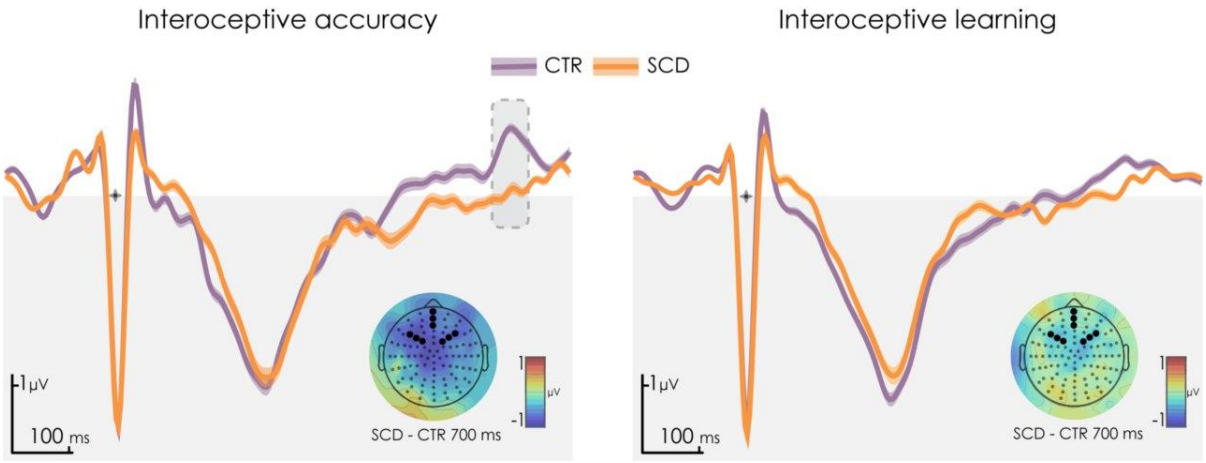
Abstract: Objectives: Neurocognitive plasticity is critical for maturation throughout adolescence. However, these adaptive processes also increase vulnerability for developing addictions. The connection between plasticity and vulnerability for addictions is not fully known. Smoked cocaine (SC) is the earliest intermediate product of cocaine hydrochloride (CC) production and represents a public health problem for teenagers in developing countries. SC is highly addictive mainly due to its fast administration route, which has been linked an increased ability to sense and process body signals (interoception). However, there is scant evidence about changes during adolescence and no report has assessed interoception in SC consumers. In this study, we implement a multimodal approach (behavioral, EEG, and neuroimaging) to study differences in interoceptive performance between adolescent consumers of SC, CC and controls (CTR).
Methods: We included 25 participants that smoked (SC), 22 that insufflated cocaine (CC), and 25 matched CTR. Cocaine consumption begun between ages 14-16. We applied a heartbeat-detection (HBD) task and measured modulations of the heart-evoked potential (HEP) during interoceptive conditions. We complemented these measures with structural (MRI) and functional connectivity (fMRI) analysis of the main interoceptive hubs (insular, ACC and somatosensory cortex).

Results: HBD and HEP results showed that only SC consumers presented ongoing psychophysiological measures of enhanced interoceptive accuracy. This pattern was associated with a structural and functional tuning of interoceptive networks.
Conclusions: Our findings provide the first evidence of an association between cardiac interoception and SC consumption in adolescents. They also support models that propose hyper-interoception as a key aspect of addiction while suggesting that this enhancement may depend on specific administration routes.



Disclosures: L.A. de la Fuente de la Torre: None. **L. Sedeño:** None. **S. Schurmann Vignaga:** None. **S. Sonzogni:** None. **C. Ellmann:** None. **A. García:** None. **M. Cetkovich:** None. **E.T. Cánepa:** None. **T. Torralva:** None. **E. Tagliazucchi:** None. **A. Ibáñez:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.05

Topic: G.08. Drugs of Abuse and Addiction

Support: Salk Women & Science Special Award

Title: Neural mechanisms for opioid-induced respiratory depression

Authors: *S. LIU[1,2], M. YE[1], M. SONG[2], S. HAN[1];
[1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]Div. of Biol. Sci., UCSD, La Jolla, CA

Abstract: Opioid drugs are the most commonly used and the most effective analgesics to treat acute and severe pain. However, the dramatic painkilling effects come with many side effects, among which opioid-induced respiratory depression (OIRD) is the major cause of death by opioid overdose. It is now the leading cause of death in the U.S., taking away 8 lives every single

hour (https://www.cdc.gov). Although this is a serious national crisis that affects public health as well as social economic welfare, research on elucidating neural mechanisms of OIRD is lacking. Here we report that conditional knockout of the *Oprm1* gene by expressing Cre recombinase in the brainstem of the *floxed-Oprm1* mice reduced the respiratory depression by systemic morphine injection. Moreover, optogenetic and chemogenetic activations of those brainstem *Oprm1*-expressing neurons increased respiration rate while their chemogenetic inhibition led to significant respiratory depression. Finally, chemogenetic activation of brainstem *Oprm1* neurons rescued morphine-induced respiratory depression. Together, these findings suggest that the brainstem *Oprm1* neurons are critical for the OIRD in mice.

Disclosures: S. Liu: None. **M. Ye:** None. **M. Song:** None. **S. Han:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.06

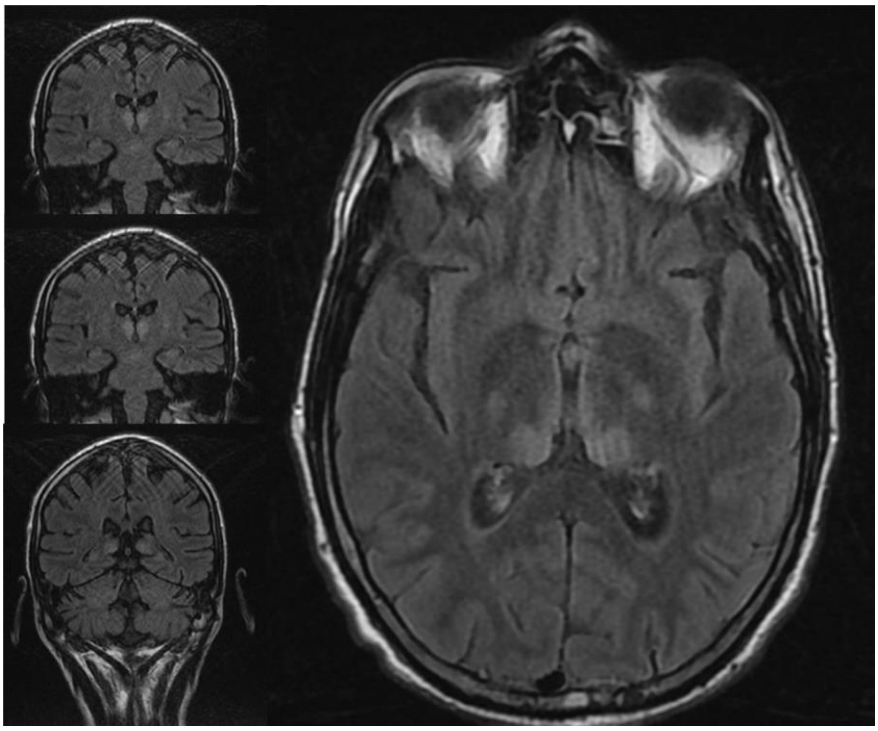
Topic: G.08. Drugs of Abuse and Addiction

Title: Heavy cannabis use associated with Wernicke's encephalopathy

Authors: *A. CHAUDHARI, Z. YING-LI, A. LONG, A. AFSHINNIK;
Univ. of California San Francisco, Fresno, CA

Abstract: Cannabis use accounts for more than 149,000 hospital visits annually. As more states legalize recreational Cannabis, side effects that are currently rare will become increasingly more common. Here, we present a rare case of Cannabis-induced hyperemesis causing Wernicke’s encephalopathy. This is an investigational case report utilizing retrospective data; all activities were consented for by the patient’s surrogate decision maker and approved by the IRB. Our 41 year old patient presented to the hospital in status epilepticus secondary to severe vomiting and hyponatremia. He was given 1 dose of thiamine, glucose and folate, and admitted to the ICU. His history was significant for remote alcohol use (1-2 beers/week about 20 years ago) and heavy marijuana use from strains grown in the patient’s own backyard. A diagnosis of Cannabis Hyperemesis Syndrome was made. Seizures resolved after correction of electrolytes, and he became awake and alert with no motor/sensory deficits. His neurological exam showed memory deficits including confabulations (e.g. incorrectly listing occupation) and delusions (e.g. praying to a queen bee). An extensive workup including blood work, infectious panels and autoimmune studies was entirely negative. Neuroimaging was significant for bilateral thalamic hyperintensities on T2 FLAIR MRI. A list of associated diagnoses, including Wernicke’s encephalopathy, extrapontine osmotic myelinolysis, Artery of Percheron infarction, and West Nile encephalitis were considered. Intravenous Thiamine was started, leading to a gradual decrease in the patient’s symptoms. He is now 2 months into rehabilitation and continues to

make progress in recalling life events. Cannabis, unlike alcohol, is presumed to induce hyperphagia and nutritional supplements are often not initiated. However, the foods ingested by Cannabis users are nutritionally deficient. In addition, Cannabis-induced vomiting can further cause malnutrition. Complications, like Wernicke's encephalopathy, can be prevented by supplementing Thiamine early in Cannabis intoxication.



Disclosures: **A. Chaudhari:** None. **Z. Ying-Li:** None. **A. Long:** None. **A. Afshinnik:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.07

Topic: G.08. Drugs of Abuse and Addiction

Title: Gabapentin induced drug seeking like behavior: Possible involvement of dopaminergic mechanism

Authors: *Y. S. ALTHOBAITI[1], A. ALGHORABI[2], H. ALMALKI[2], A. ALGHAMDI[2], A. BASFER[2];
[1]Pharmacol. and Toxicology, [2]Taif Univ., Taif, Saudi Arabia

Abstract: The abuse of prescription medications is becoming a problem in many countries. One of these medications is gabapentin which is an antiepileptic drug that can be used in several neurological and psychiatric disorders. It is marketed as an agent that has no significant risk for abuse. However, this medication was frequently reported to be abused in several case reports. This abuse could be driven by its ability to induce rewarding effects. However, its abuse potential was not investigated previously in preclinical studies. In this study, the abuse potential of gabapentin was assessed in conditioned place preference (CPP) model of drug addiction in mice. Male BALB/c mice were separated into four groups; the first group was given vehicle (1ml/kg/day, i.p.) for 8 days during the acquisition phase. The remaining groups received i.p. injections of gabapentin (100, 200, or 300 mg/kg) every other day during the acquisition phase. We also tested blocking D1 receptors by SKF-83566, a potent and selective D1-like dopamine receptor antagonist, for the first time in an animal model of gabapentin addiction. No significant change in time spent in drug-paired chamber as compared to vehicle-paired chamber in mice treated with 100 or 200 mg/kg. Interestingly, the time spent in drug-paired chamber as compared to the vehicle-paired chamber was significantly increased in mice that were treated with 300 mg/kg of gabapentin. SKF pretreatment attenuated gabapentin-induced seeking like effect, indicating the important role of D1 receptors in mediating this effect. This indicates that gabapentin can stimulate the rewarding mechanisms in the brain. These results demonstrated for the first time the abuse potential of gabapentin in animal model of drug addiction.

Disclosures: Y.S. Althobaiti: None. **A. Alghorabi:** None. **H. Almalki:** None. **A. Alghamdi:** None. **A. Basfer:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.08

Topic: G.08. Drugs of Abuse and Addiction

Support: USPHS Grant R00AA0217

Title: Chronic excessive alcohol drinking dysregulates behavior and neuropeptide signaling in rats

Authors: *S. PANDEY, J. R. BARSON;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Long term excessive alcohol drinking is a risk factor for as well as a key feature of alcohol addiction. In the addicted state, chronic excessive alcohol consumption has been linked to distinct behavioral and neurochemical alterations, which are studied as targets for intervention; however, the effects of chronic excessive alcohol consumption, prior to the onset of

addiction, have received less attention. In this study, we sought to identify changes that occur early in the history of chronic high-level voluntary ethanol consumption. Rats were given access to 20% ethanol in their home cage under the two-bottle-choice intermittent-access paradigm or were maintained on water and laboratory chow only. To assess behavioral changes, they were tested in an activity chamber, light-dark box, elevated plus maze, and open field, first while ethanol-naive and then after 8 weeks of drinking. To assess neurochemical changes, tissue from their paraventricular nucleus of the thalamus (PVT), a reward-related brain region, was obtained after 11 weeks of ethanol (or water) drinking, for analysis of mRNA using quantitative PCR. All post-drinking assessments were conducted 24 hours after an ethanol drinking session, when rats would normally begin their next drinking session. We found that, after 8 weeks of chronic ethanol access, high-drinking rats (n = 6-8; intake > 5g/kg/24hrs, preference > 40%), but not low-drinking (n = 6-8; intake < 3g/kg/24hrs, preference < 20%) or water-drinking rats (n = 6-8), spent significantly more time in the open arm of the elevated plus maze and the light side of the light-dark box when compared to their performance prior to ethanol access, suggesting that chronic excessive ethanol drinking induces a risk-taking phenotype. These high drinkers, in the anterior PVT, also showed a downregulation in the expression of the neurotensin receptor 2, a receptor previously implicated in the control of ethanol drinking, when compared to both low drinkers and controls, suggesting that chronic excessive ethanol drinking also dysregulates PVT function. Ongoing experiments are seeking to expand this neurochemical result with Western blot protein analysis. Together, these findings demonstrate that, even prior to the development of full addiction, chronic, high-level voluntary ethanol drinking induces behavioral and neurochemical changes that may perpetuate problematic drinking and eventually lead to addiction. These findings open opportunities for early interventions.

Disclosures: S. Pandey: None. **J.R. Barson:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.09

Topic: G.08. Drugs of Abuse and Addiction

Title: The role of LRRK2, a Parkinson's disease-related protein, in regulating striatal function and alcohol drinking in mice

Authors: *D. DA SILVA E SILVA[1], A. MAMAIS[2], M. R. COOKSON[3], V. A. ALVAREZ[4]; [1]NIH, Rockville, MD; [2]Cell Biol. and Gene Expression Section, Natl. Inst. On Aging, NIH, Bethesda, MD; [3]Lab. Neurogenetics, Natl. Inst. Aging, NIH, Bethesda, MD; [4]Lab. on Neurobio. of Compulsive Behaviors, Natl. Inst. on Alcohol Abuse and Alcoholism, Bethesda, MD

Abstract: Chronic alcohol exposure alters striatal function and drives compulsive alcohol-seeking despite negative consequences, one of the hallmarks of alcohol use disorders. The striatum plays a central role in goal-directed behaviors and it is thought to undergo long-lasting changes that drive addictive behaviors. We previously found that the Lrrk2 gene is upregulated in the striatum of animals that show inflexible alcohol drinking as defined by high alcohol preference even after its taste-adulteration. The Lrrk2 gene product is an AKAP that regulates PKA availability at spines and it is involved in synaptic modulation in striatal neurons. We hypothesized that the Lrrk2 gene through its modulation of PKA signaling downstream of dopamine D1 receptors (D1R) is involved in facilitating compulsive alcohol taking. To prove this hypothesis, we first tested whether alcohol drinking can modulate Lrrk2 levels in C57BL/6 mice. Using qPCR and RNAscope, we found that alcohol drinking increased mRNA levels for Lrrk2 in the dorsal striatum, in both D1R and D2R-expressing neurons, the two classes of projection neurons in the striatum. Interestingly and contrary to our prediction, alcohol reduced total protein levels for Lrrk2 in the dorsolateral striatum. To assess whether a preexisting downregulation of Lrrk2 protein levels is sufficient to change alcohol drinking, we tested different Lrrk2 cell-specific knockout mice on alcohol drinking tasks and other alcohol-related behaviors. We found that mice lacking Lrrk2 constitutively show enhanced alcohol consumption. Similarly, when the Lrrk2 gene was specifically deleted in D1R neurons, mice showed an increased and persistent alcohol consumption even after quinine adulteration compared to littermate controls. Moreover, these D1-Lrrk2-KO mice consumed more alcohol in an operant self-administration task and showed higher breakpoint, an indication of higher motivation to consume alcohol. Additionally, D1-Lrrk2-KO mice showed enhanced alcohol-induced locomotion, a response that is mediated by dopamine D1R, as well as are more sensitive to a D1-like receptor agonist. These findings suggest that Lrrk2 regulation of PKA activity downstream of D1R in direct-pathway striatal neurons plays an important role in regulating alcohol consummatory behaviors.

Disclosures: D. Da Silva E Silva: None. **A. Mamais:** None. **M.R. Cookson:** None. **V.A. Alvarez:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.10

Topic: G.08. Drugs of Abuse and Addiction

Title: The α5 nicotinic acetylcholine receptor subunit may mediate alcohol reinforcement through progesterone signaling and alteration of glycinergic and serotonergic receptors in the interpeduncular nucleus

Authors: *S. CALIGIURI[1], V. MATHIS[3], A. LEPACK[2], M. V. MICIONI DI BONAVENTURA[4], M. HEYER[5], P. BALI[5], Q. LU[7], A. RAMAKRISHNAN[6], I. MAZE[6], R. M. O'CONNOR[8], P. J. KENNY[9];
[2]Neurosci., [1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Icahn Sch. of Med. At Mt Sinai, New York, NY; [4]Univ. of Camerino, Sch. of Pharmacy, Pharmacol. Unit, Camerino, Italy; [5]Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Icahn Sch. of Med. at Mount Sinai, NY, NY; [7]Scripps Inst., New York, NY; [8]Icahn Sch. of Medicine, Mount Sinai, New York, NY; [9]Dept. of Pharmacol. and Systems Therapeut., ICAHN Sch. of Med. At Mount Sinai, New York, NY

Abstract: Introduction: Single nucleotide polymorphisms for CHRNA5, the gene encoding the alpha5*nicotinic acetylcholine receptor (nAchR) subunit, increase the risk for tobacco and alcohol co-dependence. To enhance our understanding of this subunit in alcohol reinforcement, we utilized alpha5*nAchR knockout models in a sex and brain region specific manner.
Methods and Results: Male and female global CHRNA5 KO and WT littermates were trained on a fixed ratio-3 and a progressive ratio schedule of self-administration for varying doses of ethanol (2.5, 5, 10, 20%) or 5% sucrose (control) (n=60). Female WT mice earned on average 63% more self-administered ethanol rewards and exhibited higher blood alcohol levels versus global alpha5*nAchR KO females ($p<0.05$). In contrast, WT and KO males were indistinguishable. The sex specific phenotype may be through hormonal regulation. An injection of progesterone enhanced ethanol self-administration in WT females but not in CHRNA5 KO females or in males. Utilizing FLIPR, progesterone alone induced a higher calcium signal in alpha5 HEK cells versus other nicotinic or HEK cells. Progesterone treatment induced robust c-fos in the interpeduncular nucleus which partially co-localized to VGAT. Silencing of IPN VGAT neurons through HM4 DREADD manipulation reduced ethanol self-administration and blood alcohol in female mice. CRISPR technology was developed to locally KO alpha5*nAChRs in the IPN with a 15% *in vivo* mutation rate. Local KO of CHRNA5 in the IPN significantly reduced ethanol self-administration and blood alcohol levels versus female mice with intact CHRNA5 in the IPN. A rescue of hsCHRNA5 in the IPN of CHRNA5 KO females increased ethanol self-administration and blood alcohol levels. Local KO of CHRNA5 in the IPN attenuated the progesterone enhanced ethanol self-administration phenotype. RNA-seq of the interpeduncular nucleus identified SLC6A4, SLC6A5, and TPH2 as lower in the CHRNA5KOs versus WTs. Manipulation of local SLC6A4, SLC6A5, and TPH2 via siRNA is currently underway.
Conclusion: Female binge drinking is an arising issue with severe physiological and psychological sequelae. We identified that CHRNA5 and VGAT expressing neurons of the IPN may regulate the behavioral response to progesterone and enhance ethanol reinforcement in female mice. CHRNA5 KO may disturb glycine and serotonergic receptors and may modulate IPN signaling machineries.
Funding: National Institutes of Health and the Canadian Institutes of Health Research

Disclosures: S. Caligiuri: None. **V. Mathis:** None. **A. Lepack:** None. **M.V. Micioni Di Bonaventura:** None. **M. Heyer:** None. **P. Bali:** None. **Q. Lu:** None. **R.M. O'Connor:** None. **P.J. Kenny:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH

Title: Alcohol metabolism directly fuels histone acetylation in the brain

Authors: *P. MEWS[1], G. EGERVARI[2], R. NATIVIO[2], S. SIDOLI[2], G. DONAHUE[2], B. A. GARCIA[2], E. J. NESTLER[1], S. L. BERGER[2];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Perelman Sch. of Med. at the Univ. of Pennsylvania, Philadelphia, PA

Abstract: In the adult brain, epigenetic control of gene expression has important roles in the processing of neural activity. Emerging evidence suggests that epigenetic regulation is dependent on the metabolic state, implicating metabolic factors in neural functions and behavior. We previously showed that neuronal gene expression programs are driven by local production of acetyl-CoA fueling histone acetylation. Notably, breakdown of alcohol in the liver rapidly increased blood acetate, the key the substrate used by acetyl-CoA synthetase (ACSS2) to produce acetyl-CoA in neurons. However, it remains unclear whether hepatic alcohol metabolism affects histone acetylation in the brain. To determine whether hepatic acetate from alcohol breakdown fuels dynamic histone acetylation in neurons, we employed stable isotope labeling to track isotopically labeled ethanol in mice. Employing advanced quantitative mass spec technology and metabolomics, we analyzed the contribution of heavy-labeled alcohol to newly catalyzed histone acetylation in the brain following *i.p.* injection. Further, to investigate the role of ACSS2 for alcohol-derived acetylation, we attenuated ACSS2 expression in the dorsal hippocampus and performed additional mass spec and RNA-sequencing to survey gene expression genome-wide. Here, we demonstrate that alcohol-derived acetyl-groups rapidly fuel dynamic histone acetylation in the brain, and that the incorporation of alcohol carbons into histone acetylation is dependent on neuronal ACSS2 expression. Our data reveal that increasing acetate from alcohol metabolism is activated by ACSS2, a process we illustrate to readily manipulate key gene-regulatory histone acetylation linked to neural function. Moreover, we show genome-wide that alcohol-induced gene expression is dependent on catalytic ACSS2, *in vivo* in the hippocampus. In addition, using a small molecule inhibitor to catalytic ACSS2 (ACSS2i), we found that ACSS2i-sensitive genes that are regulated by acetate in hippocampal neurons are related to learning and memory. Together, our findings establish a novel between alcohol metabolism and neuronal histone acetylation, providing the first evidence for dynamic signaling from alcohol metabolism directly to epigenetic regulation in neurons. Our data further

implicate that other peripheral sources of physiological acetate, primarily the gut microbiome, may similarly affect neuronal histone acetylation and brain function. Therefore, this novel mechanism of neuro-epigenetic regulation by metabolic ACSS2 may pave the way to novel therapeutic interventions in alcohol addiction and other neuropsychiatric disorders.

Disclosures: **P. Mews:** None. **G. Egervari:** None. **R. Nativio:** None. **S. Sidoli:** None. **G. Donahue:** None. **B.A. Garcia:** None. **E.J. Nestler:** None. **S.L. Berger:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant 5R01AA024774 (HNR)

Title: Effect of alcohol drinking on myelinating cells in male and female mice

Authors: *S. AKLI, S. P. SCOTT, S. NOUDURI, F. L. REAGAN, R. SENTHILKUMAR, H. N. RICHARDSON;
Psychological and Brain Sci., Univ. of Massachusetts, Amherst, MA

Abstract: The prefrontal cortex is important for emotional regulation, decision-making, and impulse control, and it continues developing throughout adolescence. Myelination is a process in which a lipid-rich projection wraps axons, leading to rapid and efficient neural communication. Oligodendrocytes are the glial cells responsible for myelinating axons in the central nervous system. We found that voluntary binge drinking early in adolescence reduces myelinated fiber density in the prefrontal cortex of male rats. Other studies have shown that injections of high doses of alcohol damage myelin and reduce myelin-related proteins in adolescent mice. The goal of the current study was to determine if voluntary alcohol drinking reduces myelin in adolescent mice and to gain insight into the mechanisms by which alcohol impacts myelin. We hypothesized that alcohol targets mature oligodendrocytes, resulting in a reduction in oligodendrocyte cell number and a decreased myelinated fiber density. To test this, male and female mice were exposed to voluntary alcohol drinking using the drinking in the dark (DID) procedure throughout adolescent development. Beginning on postnatal day 28, mice were allowed access to unsweetened 20% ethanol solution for 2 hours on day 1-3 and for 4 hours on day 4 followed by 3 days of withdrawal per cycle for a total of 4 cycles in 4 weeks. Our data suggest that alcohol drinking reduces prefrontal myelin density in mice, similar to what we observed in drinking rats. Contrary to our hypothesis, reduced myelinated fiber density does not appear to be due to a measurable decrease in mature oligodendrocytes in the corpus callosum of male mice. However, high variability in this measurement suggests that our ability to isolate

individual cells from one another for accurate quantification may need further refinement. In addition, to further elucidate how alcohol impacts oligodendrocyte lineage, we are using a transgenic approach that allows in vivo tracking of oligodendrocyte lineage cells in a time-dependent manner. Overall these studies will determine the effect of alcohol on the regulation of oligodendrocyte differentiation during adolescent myelination of prefrontal axons in the murine brain.

Disclosures: S. Akli: None. **S.P. Scott:** None. **S. Nouduri:** None. **F.L. Reagan:** None. **R. Senthilkumar:** None. **H.N. Richardson:** None.

Nanosymposium

109. Neural and Molecular Mechanisms of Alcohol and Substance Use Disorders

Location: Room S106

Time: Sunday, October 20, 2019, 8:00 AM - 11:15 AM

Presentation Number: 109.13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA022538
NIH Grant AA05846

Title: The KCNK13 potassium channel is a target for alcohol-induced activation of neurons in the ventral tegmental area

Authors: C. YOU[1], B. J. VANDEGRIFT[1], D. HE[2], T. TEPPEN[2], A. A. PRADHAN[2], A. F. TIPTON[3], S. C. PANDEY[2], A. W. LASEK[2], ***M. S. BRODIE**[1];
[1]Physiol. and Biophysics / Ctr. for Alcohol Res. in Epigenetics, [2]Psychiatry / Ctr. for Alcohol Res. in Epigenetics, [3]Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: The ventral tegmental area (VTA) is highly involved in incentive and behavioral motivation through dopaminergic projections to various brain regions including components of the central reward/reinforcement system, and plays a major role in addiction and alcoholism. VTA dopaminergic (DA) neurons are known to be activated by alcohol, both *in vivo* and *in vitro.* However, the precise target of alcohol that mediates excitation of VTA neurons has not been identified. We have shown that quinine and quinidine block ethanol excitation of VTA neurons, suggesting to us that two-pore “leak” potassium channels sensitive to these agents could be involved in ethanol excitation. We have published evidence that KCNK13, a two-pore “leak" potassium channel mediates at least a portion of ethanol excitation of VTA neurons of C57BL/6J mice (You *et al.*, 2019). We have now further examined the role of KCNK13 in ethanol excitation of VTA neurons from rats. As in mouse VTA neurons, isoflurane excited VTA neurons from Fisher344 rats. Gadolinium chloride (20-100 µM) antagonized ethanol and isoflurane excitation of rat VTA neurons. Immunohistochemical studies indicated an abundant presence of KCNK13 in tyrosine hydroxylase (TH) positive and TH negative neurons of the

VTA from both Sprague-Dawley and Fisher344 rats. Following exposure to interference RNA (RNAi) targeting *Kcnk12* or *Kcnk13*, extracellular electrophysiological recordings of VTA neurons indicated a significant reduction of ethanol excitation of VTA neurons exposed to RNAi targeting *Kcnk13* but not RNAi targeting *Kcnk12*. We also found that expression of *Kcnk13*, but not *Kcnk12* in the VTA of rats was increased one hour after an acute ethanol injection. Interestingly, there was a significant increase in *Kcnk13* mRNA at 24h of withdrawal from Lieber-DeCarli ethanol diet, but a significant decrease in *Kcnk13* mRNA at 72h of withdrawal. Decreased *Kcnk13* in the VTA is associated with increased ethanol intake (You, *et al.*, 2019). These results further support a role for KCNK13 as a novel alcohol-sensitive molecule in VTA neurons, and that KCNK13 may represent a unique and important target for development of a pharmacotherapy for alcoholism treatment. Supported by PHS grant AA022538.

Disclosures: C. You: None. **B.J. Vandegrift:** None. **D. He:** None. **T. Teppen:** None. **A.A. Pradhan:** None. **A.F. Tipton:** None. **S.C. Pandey:** None. **A.W. Lasek:** None. **M.S. Brodie:** None.

Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.01

Topic: H.01. Animal Cognition and Behavior

Support: NEI R01EY017699
NIMH R01MH064043
Silvio O. Conte Center - 1P50MH109429

Title: Functional interactions between LIP and V4 during rhythmic environmental sampling

Authors: *M. K. ERADATH[1], S. KASTNER[1,2];
[1]Princeton Neurosci. Inst., [2]Dept. of Psychology, Princeton Univ., Princeton, NJ

Abstract: Attention is not a stationary process but involves rhythmic sampling of the environment, characterized by alternating periods of increased or decreased perceptual sensitivity, occurring at a rate of 3-5 Hz. Recent electrophysiological evidence has begun to provide a neural basis for rhythmic sampling by showing alternating attentional states in the fronto-parietal network, linked to different phases of theta activity. For example, during a covert attention task, periods of enhanced gamma and beta activity and increased perceptual sensitivity alternate with periods of enhanced alpha activity and decreased perceptual sensitivity at the attended spatial locations. However, the functional interactions between visual cortex and fronto-parietal cortex during rhythmic sampling are unknown. Here, we explored functional interactions between LIP and V4 during the rhythmic environmental sampling, by conducting simultaneous

electrophysiological recordings from LIP and V4 of macaque monkeys performing a covert visual spatial attention task that measured rhythmic sampling. Preliminary electrophysiological results show a relationship between the phase of theta (5 Hz) activity in V4 and detection performance, similar to what has previously been shown in LIP and FEF, thereby suggesting a role of theta oscillations in coordinating neural activity in sensory cortex as well as in fronto-parietal network. An increased theta-gamma phase-amplitude coupling was observed between V4 and LIP during periods of increased perceptual sensitivity, indicating a rhythmic theta-dependent visual input to the fronto-parietal attention network during the cue-target delay period. Previous work has shown enhanced alpha activity in LIP during periods of decreased perceptual sensitivity, which has been interpreted as a mechanism of suppression of visual processing at a cued location during periods of attentional shifts. The current results show an increase in alpha (7-14 Hz) - gamma (40-60 Hz) phase-amplitude coupling between LIP and V4 during the periods of increased detectability, suggesting an alpha mediated functional coupling between LIP and V4, independent of the alpha mediated suppression observed during periods of attentional shifts. Our preliminary results suggest a role of theta oscillations in coordinating visual inputs to the fronto-parietal network via an alpha mediated cortical suppression or enhancement in different phases of theta during rhythmic environmental sampling.

Disclosures: **M.K. Eradath:** None. **S. Kastner:** None.

Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.02

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI 15H05374
JSPS KAKENHI 18K19492
JSPS KAKENHI 19H05007
Takeda Science Foundation
Council for Addiction Behavior Studies
The Ichiro Kanehara Foundation

Title: Population dynamics in signaling expected values across multiple reward-related brain regions

Authors: *H. YAMADA[1], Y. IMAIZUMI[2], M. MATSUMOTO[2,3];
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Abstract: Previous literature indicates that many brain regions are involved in reward-based decision makings by signaling expected values (i.e., probability times magnitudes). However, the nature of the signals is poorly understood in terms of temporal dynamics of the expected value signals carried by the neuronal population, and their differences among reward-related brain regions. To this end, we examined the following question in multiple reward-related brain regions: whether the expected value signals appeare stable or instantaneous during the presentation of the cue stimuli. We used simple cued task, in which the expected values of stimulus was indicated by pie-chart visual stimuli to the monkeys with a great precision; 0.1 to 1.0 probability of fluid rewards by 0.1 increment and 0.1 ml to 1.0 ml magnitude of rewards by 0.1 ml increment. This enables us to map out the neuronal activity in the space of probability and magnitude of rewards (i.e., expected values) from the onset to offset of the cue stimuli. During the presentation of the cue stimuli, we recorded 686 neurons from two monkeys of four brain regions that are known to process reward information: the dorsal striatum (DS, 194), ventral striatum (VS, 144), central part of the Orbitofrontal cortex (OFC, area 13M, 190), and medial part of the Orbitofrontal cortex (mOFC, area 14O, 158). First, a conventional linear regression analysis to detect expected value modulation as probability and magnitude revealed that all four brain regions carry signals of expected values and its component (i.e., probability or magnitude) as a mixture on the population ensemble activities. By using a principle component analysis (PCA) similar to the state-space analysis (Monte et al., 2013), we found that the cOFC and VS populations maintain stable expected values signals moment-by-moment through the symbol presentations. Although the expected values signals coexisted among four populations in a moment after the symbol presentations, these signals evolved in an order of the cOFC, followed by VS and DS, and lastly mOFC. These population ensembles indicate that the detection and integration of probability and magnitude reflect a sequential process embedded in multiple brain regions, and potentially provide general framework toward understanding the expected values computation through reward circuitry.

Disclosures: H. Yamada: 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.; Council for Addiction Behavior Studies, This is for examining gambling behavior. **Y. Imaizumi:** None. **M. Matsumoto:** None.

Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.03

Topic: H.01. Animal Cognition and Behavior

Title: Is it stable or dynamic? Value representation in the OFC and ACC over an extended delay

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Abstract: Optimal decisions require us to keep track of the value of different choice options. When the outcome is delayed, updating the value of an option requires us to temporarily hold the value of that option in memory to compare it with the actual outcome. The orbitofrontal (OFC) and anterior cingulate (ACC) cortices have been shown to represent the value of expected and received outcomes, however little is known about the dynamics of value representation in these areas over an extended delay. In other areas of prefrontal cortex that specialize in holding information online across delays, there has been debate about whether this information is maintained by stable or dynamic neural representations. Here we extend these ideas to investigate the dynamics of neural representations of value in a value-based decision making task. Neurons were recorded in the OFC and ACC of two monkeys while they viewed visual cues associated with a later reward. In light of the recent debate about working memory representation and dynamics, we contrasted two approaches to understand the dynamics of value representations over time. First, we used cross-temporal decoding from the population of neurons and found that value representations appeared dynamic, utilizing different population codes at different times during the delay. Second, we defined a subspace of the same population activity that selected for stable representations of value. Here we found value representations to be extremely stable. Further, we show that single neuron encoding strength and stability are correlated with contribution to the subspace. Thus, using methods developed in opposite theoretical contexts, we show that at the unit and population level, representation is both sequential (dynamic) and persistent (stable). This type of mixed coding is likely critical for the brain to represent information across delays, while being sensitive to the passage of time. While these results demonstrate that the dynamics of value representation in these areas is a matter of perspective and methods, they also show that representations in prefrontal areas are likely to be hybrid and highly complex, and cannot be described by a mere categorization approach.

Disclosures: P. Enel: None. **J.D. Wallis:** None. **E.L. Rich:** None.

Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.04

Topic: H.01. Animal Cognition and Behavior

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Title: Causal role of the lateral orbitofrontal cortex in credit assignment

Authors: *D. FOLLONI[1], E. FOURAGNAN[2], M. WITTMAN[1], L. ROUMAZEILLES[1], L. TANKELEVITCH[1], L. VERHAGEN[1], J. SALLET[1], M. F. S. RUSHWORTH[1];
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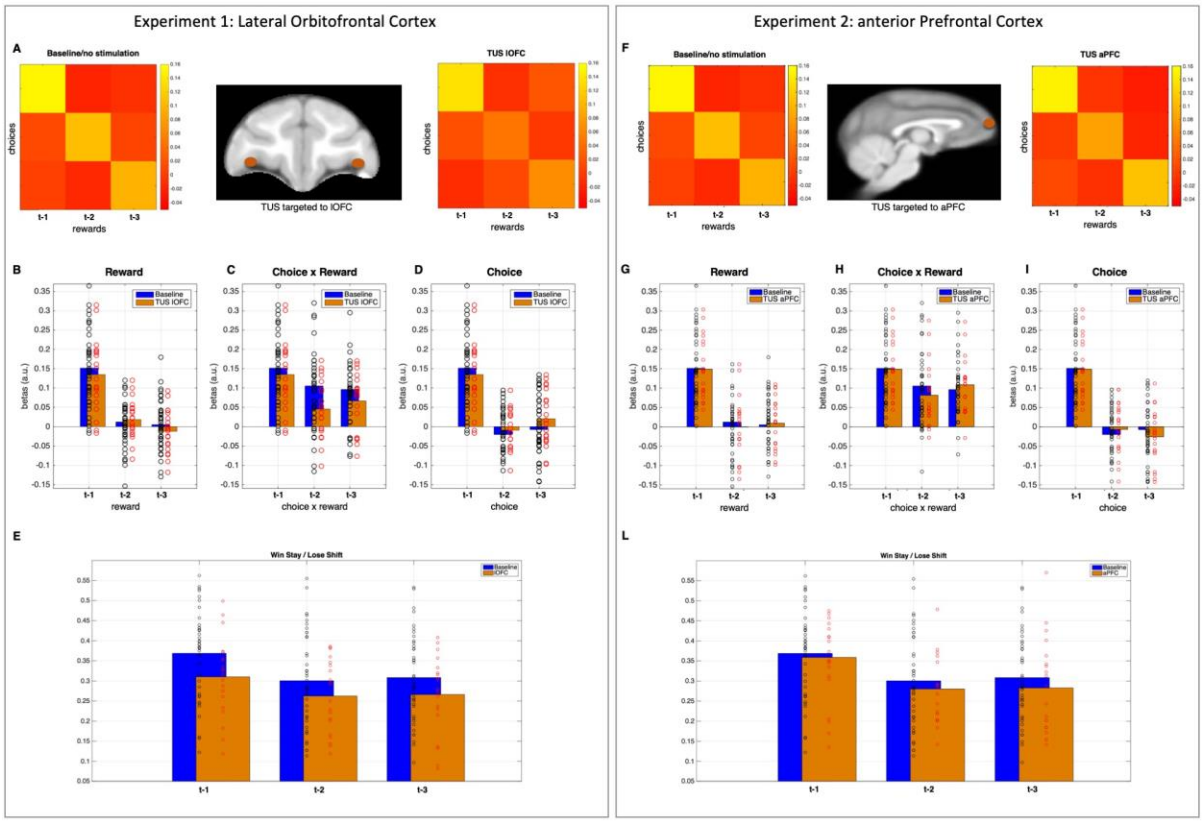
Abstract: Introduction: Adaptation to a volatile environment requires being able to flexibly learn contingent associations between choice options and outcomes to guide subsequent behavior. This type of learning is often referred to as "credit assignment" (CA). FMRI studies suggest that the lateral orbitofrontal cortex/area 12o (lOFC) plays a key role in CA. However, to determine whether such region is truly necessary for CA, the impact of its disruption must be assessed. Methods: Focused Transcranial Ultrasound Stimulation (TUS) allows to transiently disrupt neural activity in a specific brain area with high spatial focality (Folloni et al., 2019) and was here applied to 4 macaque monkeys while they performed a probabilistic three-arm reversal learning bandit task. The ultrasound wave frequency was set to the 250 kHz resonance frequency and 30 ms bursts of ultrasound were generated every 100 ms for 40 seconds. TUS was applied either to the lOFC bilaterally (experiment 1) or to a control region, the anterior prefrontal cortex (aPFC; experiment 2) immediately before the animals performed the task and compared with no stimulation (baseline) sessions. Results: After lOFC TUS, the animals showed a deficit in the encoding of CA (A). Animals were able to independently encode either choices or outcomes alone (B,D) but were impaired in learning their contingent relationships. These effects were primarily present when the impact of learning from recent trial outcomes was considered (A, C). Specifically, TUS disrupted the animals' ability to update their estimate of a choice option's value after trials in which a reward was received ("win") for choosing it but not in trials in which reward was not obtained ("lose"; E). Conversely, animals were not impaired in CA after aPFC TUS (F). APFC TUS did not affect animals' ability to adapt their behavior after "win" or "lose" trials (F-L). Conclusion: These results suggest that solely lateral OFC TUS affects credit assignment, therefore supporting evidence of a causal role of primate lOFC in forming stimulus-outcome associations based on the history of past outcomes.



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Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.05

Topic: H.01. Animal Cognition and Behavior

Support: ZIA-DA000587

Title: The orbitofrontal cortex is necessary for novel but not established economic choice

Authors: ***M. P. H. GARDNER**[1], D. SANCHEZ[2], J. ZHOU[3], J. C. CONROY[2], G. SCHOENBAUM[4];
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Abuse, IRP, Baltimore, MD; [4]Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD

Abstract: There is now a large body of work implicating the lateral orbitofrontal cortex (OFC) in economic decision-making. Yet the precise role that OFC plays in such value-based decisions is not entirely clear. Correlative studies indicate that OFC neurons identify the most valuable option and drive its selection (Padoa-Schioppa et al. 2006, Rich et al. 2016). However several causal studies by our lab have failed to find any signs of disrupted behavior in rats performing a task modeled after these recording studies (Gardner et al. 2017). Leaving aside potential species differences, one possible explanation for this dichotomy is that the OFC is only involved in establishing the goods space, but not for exploiting it during ongoing behavior. By this logic, the neural correlates would reflect ongoing monitoring of the use of an established goods space, monitoring which would only be necessary when that goods space is first established or when new information appears that must be integrated into the space. Here we tested this hypothesis by optogenetically inactivating the OFC in rats trained to perform the same monkey-inspired economic choice task used in our prior published work. On critical test days, rats were presented with choices between two different foods well-known to the rats, but which the rats had never specifically chosen between in the past. We then bilaterally inactivated orbitofrontal cortex (both the lateral and medial OFC) the first time rats chose between the two different foods using halorhodopsin to inhibit activity in these areas. Inactivation of OFC substantially disrupted the rats' ability to quickly achieve a stable preference for the two foods over the course of the session. These results are consistent with the theory that OFC can be important for economic decision-making, however they are not in accord with the proposal that this area is the only or even primary region involve in evaluating the utility of available options. Instead they indicate that the critical role of the OFC is to form and subsequently adjust the goods space used by other areas to make the choice, when information about new experiences must be incorporated - a theory which is in accordance with recent OFC inactivation data from rats performing the Daw two-step task (Miller et al. 2018).

Disclosures: M.P.H. Gardner: None. **G. Schoenbaum:** None. **D. Sanchez:** None. **J.C. Conroy:** None. **J. Zhou:** None.

Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.06

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 2R01N086104

Title: Primate insular cortex represents contextual information that modulates risk-attitude

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Abstract: Uncertain decisions are strongly influenced by risk-attitude. In humans, risk-attitude is flexible and depends on contextual factors, such as whether the outcomes represent gains or losses, and the current wealth level. However, the neural mechanisms underlying these effects are not known. To investigate these questions, we designed a risk-based decision-making task, in which monkeys had to choose between a sure option with certain outcome and a gambling option with uncertain outcome with different explicitly indicated probabilities. Critically, the monkeys were trained to accept token as a secondary reinforcer. Across multiple trials, they had to accumulate six tokens to earn a standard fluid reward. This allowed us to test gamble options that resulted in a gain or loss of token and to test the effect of different token assets on the preference for the same gamble option. Our behavioral results showed that the risk-attitude of the monkeys was both influenced by the gain/loss domain and by the currently accumulated token number. The monkeys showed an overall tendency of risk-seeking in both the gain and the loss domain. However, they displayed more preference for the gamble option when facing a risky gain than when facing a risky loss. In addition, we found an effect of token assets at the start of a trial on choice behavior. This effect varied in the gain and the loss domain. With increasing token assets, monkeys were prone to choose the gamble option less often in the gain domain, but more or equally often in the loss domain. To study the neuronal mechanisms underlying this results, we recorded from neurons in the anterior insular cortex (AIC). We found that many AIC neurons encode the wealth level of the monkey, i.e. the token number at the start of trial. In addition, we found that many AIC neurons encode, whether the offers represented a gain or a loss. Some of them encoded the contextual difference between gain and loss in a binary manner. Other neurons represented a context-specific value signal. These neurons encoded the expected value of options in a parametrical manner, but asymmetrically, only in the gain or loss domain. These gain/loss context signals and wealth level signals were present before the decision was made. Furthermore, we found that trial-by-trial fluctuations of these token- and gain/loss-encoding neurons were significantly correlated with fluctuations in the monkey's risk-attitude. In sum, our behavioral findings indicate that the monkey's choices depend heavily on their relative changes in wealth (gain or loss), as well as wealth level. Our neural data indicate an important role of AIC in monitoring contextual factors that influence risk attitudes.

Disclosures: Y. Yang: None. **X. Li:** None. **V. Stuphorn:** None.

Nanosymposium

110. Representations of Value and Economic Choice Across Different Brain Regions

Location: Room N427

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 110.07

Topic: H.01. Animal Cognition and Behavior

Support: John Templeton Foundation

Title: The effects of dopamine and episodic future thinking on intertemporal choice in Parkinson's disease

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Abstract: The ability to forego immediate benefits to prioritize future outcomes is central to many important life decisions and the determinants of such choices are likely multifarious. Several studies have focused on the role of dopamine in intertemporal choice, showing that increased dopamine levels are associated with more patient choices. It has been suggested that such findings may be related to a broader role for dopamine in future-oriented goal-directed behavior. A separate body of work has revealed that hippocampal-dependent episodic future thinking is also associated with more patient intertemporal choices as well as future-oriented prospective cognition. Together, these findings raise the possibility that episodic future thinking may specifically affect intertemporal choice through dopaminergic mechanisms, but the potential role of dopamine in these processes has not been examined.

Here we sought to assess the potential overlapping contributions of dopamine and episodic future thinking in intertemporal decision making. We tested patients with Parkinson's disease (n=27) both on and off their dopaminergic medication and healthy controls (n=30) on intertemporal choices, under two conditions: (i) Standard intertemporal decisions required choices between smaller sooner rewards and larger rewards delivered in the future, and (ii) episodic future thinking trials required participants to imagined a specific future scenario in which they would spend the future reward amount prior to making their choices.

We found that both episodic future thinking and dopamine medication increased patient choices. On standard intertemporal choice trials, PD patients made more farsighted choices when ON than when OFF dopaminergic medications ($p=0.03$), but on episodic future thinking trials PD patients did not differ ON vs. OFF medication, as episodic future thinking increased farsighted choice overall ($p <0.001$). These results indicate that both dopamine and episodic future thinking contribute independently to farsighted choice and may each represent distinct paths to enhance the value, or salience, of future outcomes.

Disclosures: K.E. Foerde: None. **L. Lawson:** None. **D. Shohamy:** None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

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Topic: H.02. Human Cognition and Behavior

Support: NIH 2018 R01 MH
NIH 2019 R44 NS

Title: Non-invasive mapping of acoustic-phonetic speech features in human superior temporal gyrus using ultra-high field 7T fMRI

Authors: *J. D. TOWNSEND[1], H. G. YI[4], A. BECKETT[2], M. K. LEONARD[5], A. T. VU[7], E. F. CHANG[6], D. FEINBERG[3];
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Abstract: Invasive electrocorticography (ECoG) has shown that speech is encoded in human superior temporal gyrus (STG; non-primary auditory cortex) as acoustic-phonetic features in local neural populations. To date, observing this encoding requires invasive neurophysiology to achieve high spatiotemporal resolution. However, this limits our ability to study these speech phenomena to neurosurgical patients and only to specific areas of the exposed cortical surface. Here, we develop novel methods using ultra-high field (7T) fMRI to provide non-invasive mesoscale characterization of speech features at spatial resolution sufficient for cortical layer-specific analyses. A major challenge in achieving this goal is to maximize spatiotemporal resolution while maintaining a sufficient temporal signal-to-noise ratio (tSNR) and contrast-to-noise ratio (CNR), within an experimental time-frame that is feasible for human volunteers and patient populations. fMRI data were collected on a Siemens 7T Magnetom scanner. Participants listened to naturally spoken English sentences that have been previously used to map phonetic features using ECoG (Mesgarani et al., 2014). A block design (12s on-12s off) was used, alternating between rest and randomly selected sentence blocks (2 blocks per phonetic feature condition: sonorant, plosive, fricative; 6 total) and spectrally-rotated acoustic control blocks (6 total). In Experiment 1, we measured tSNR maps to compare multi-band (MB2) EPI sequences varying acceleration factor (IPAT 3 v. 4) and partial Fourier factor 5/8 v. 6/8 v. 7/8 (TR=1000ms; 30 slices, 1mm isotropic). In Experiment 2, we compared tSNR and CNR maps while varying voxel size (1mm v 0.8mm isotropic), TR (1000ms v 2000ms), dielectric pad placement and length of acquisition. fMRI data were analyzed using FEAT in FSL 5.0 (no smoothing; results retained in native space). First, we found that MB2 IPAT3 5/8 partial Fourier had the best tSNR high spatiotemporal resolution trade-off of parameters tested. Based on this, we achieved sufficient CNR to resolve encoding of major phonetic features at the level of individual voxels in under 30 minutes of functional runs (0.8mm isotropic; TR=1000ms). These results demonstrate proof-of-concept for non-invasive high-resolution speech mapping, which will be useful for understanding the functional mesoscale organization of human speech cortex and applying this understanding to neurosurgical populations.

Disclosures: **J.D. Townsend:** A. Employment/Salary (full or part-time):; Advanced MRI Technologies. **H.G. Yi:** None. **A. Beckett:** A. Employment/Salary (full or part-time):; Advanced

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Nanosymposium

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Location: Room S402

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.02

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS098981

Title: A spatiotemporal map of reading in the ventral pathway

Authors: *O. WOOLNOUGH[1], C. DONOS[1], P. ROLLO[1], S. FISCHER-BAUM[2], S. DEHAENE[3], N. TANDON[1];
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Abstract: Visual word reading is believed to be performed by a hierarchical system with increasing sensitivity to complexity, from letters to morphemes and whole words, progressing anteriorly along the ventral cortical surface and culminating in the visual word form area (VWFA). The VWFA has been implicated in sub-lexical processing but its precise role remains controversial. The lack of temporal resolution in functional imaging studies has led to an incomplete understanding of the functional roles of visual word regions. Here, we used direct recordings across the ventral visual pathway in a large cohort to create a spatiotemporal map of visual word reading.
Word reading experiments were performed by 48 patients undergoing semi-chronic implantation of intracranial electrodes for localising pharmaco-resistant epilepsy. Each patient performed a set of experiments testing sub-lexical processing (false-fonts, letter strings of varying sub-lexical complexity and words), lexical processing (single word reading of words and pseudowords), and higher order language (jabberwocky and real sentences). Broadband gamma activity (70-150Hz) from electrodes localised to the ventral cortical surface (n>600) was used to index local neural processing.
We found, (i) contrary to fMRI studies, no evidence of a posterior-to-anterior complexity gradient but instead a sharp transition between preferential activation to false-fonts and a word selective region in the mid-fusiform. (ii) Contrasts of real and jabberwocky words during tasks requiring word engagement revealed two lexical processing regions: mid-fusiform and lateral occipitotemporal gyrus. However, no distinctions of this kind were seen while passively viewing the words in a pattern detection task, thereby suggesting task related modulation of these regions

by higher language areas. (iii) During sentence reading, activity in the mid-fusiform was driven primarily by word frequency and to a lesser extent by word length. The frequency effect was also evident in occipitotemporal gyrus, to a lesser extent, establishing in both regions ~160 ms after word onset.
In conclusion, we have identified and characterised at least two spatially separable ventral word regions that perform distinct roles in reading: lateral occipitotemporal gyrus and mid-fusiform cortex. We have shown these regions are task modulated and sensitive to the statistics of natural language, reflecting diverse influences from bottom-up vs top-down processes. This highlights the critical need for evaluating network behaviour rather than purely local activation when characterising language processes.

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Nanosymposium

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Presentation Number: 111.03

Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (31671172)

Title: Effects of musical training on white matter diffusivities and speech in noise perception

Authors: *Y. DU, X. LI;
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Abstract: Musical training is related with pervasive brain plasticity. However, evidence linking specific neural reorganization with certain behavioral advantage after musical training is still lacking. Musicians show improved speech perception in noisy environments which is suggested to be related with strengthened sensorimotor integration. Although studies have found that musicians and non-musicians differed in morphology of white matter tracts implicated in sensorimotor interaction, none has examined whether and how those white matter changes are associated with speech in noise (SIN) perception. In this diffusion tensor imaging (DTI) study, deterministic tracking was used to attain the diffusivities of two representative tracts and their subcomponents which connect sensory and motor regions, the superior longitudinal fasciculus (SLF), and corpus callosum (CC), in musicians (n = 14) and non-musicians (n = 14). Partial correlations were used to test the associations between white matter diffusivities showing significant group difference and syllable-in-noise identification accuracy. Mediation analyses further tested whether the BOLD response in right superior temporal gyrus (STG), an area that showed significant group difference and correlated with SIN accuracy in musicians in our

previous study, mediated the association between the diffusivity values of the right SLF and SIN (diffusivity-BOLD-SIN). Compared with non-musicians, musicians had higher fractional anisotropy (FA) values in the right arcuate fasciculus (AF, directly connecting STG and inferior frontal gyrus), orbital and anterior frontal portions of CC, lower radical diffusivity (RD) values in the left anterior of SLF and orbital portion of CC. Higher FA and lower RD values in those tracts correlated with better SIN performance after controlling for hearing level, auditory working memory and non-verbal IQ. Mediation analyses showed an indirect effect for the FA value of right AF in predicting SIN accuracy, where the right STG BOLD activity played a full mediation role. Our findings suggest that the white matter reorganization in the right AF, left anterior of SLF, orbital and anterior frontal of CC, which connect intra- and inter-hemispherical sensorimotor regions, may serve as a neural foundation of musician advantage in understanding speech in noise. Furthermore, we revealed the relationship between white matter plasticity, immediate hemodynamic response and behavior by showing that stronger diffusivity of the right AF may drive more efficient neural activity in right auditory cortex which in turn contributes to improved speech perception at noisy situations in musicians.

Disclosures: **Y. Du:** None. **X. Li:** None.

Nanosymposium

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NIH Grant DP1-HD091948
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Title: Narratives: fMRI data for evaluating models of naturalistic language comprehension

Authors: *S. A. NASTASE[1], Y.-F. LIU[3], H. HILLMAN[1], A. ZADBOOD[1,2], L. HASENFRATZ[1,2], N. KESHAVARZIAN[1], J. CHEN[3], C. J. HONEY[3], Y. YESHURUN[4], M. REGEV[5], M. NGUYEN[2], C. H. C. CHANG[1], C. BALDASSANO[6], O. LOSITSKY[7], M. A. CHOW[8], Y. C. LEONG[9], P. P. BROOKS[1], A. GOLDSTEIN[1], G. CHOE[1], K. A. NORMAN[1,2], U. HASSON[1,2];
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Abstract: How does the human brain construct narratives from a sequence of spoken words? Here we present a benchmark fMRI dataset for evaluating neural models for naturalistic speech perception and narrative comprehension. The 'Narratives' collection comprises over 500 scanning runs across more than 300 subjects. The story stimuli comprise over 20 spoken narratives ranging from 3 minutes to ~1 hour in duration, for ~4.5 hours of unique stimuli. Overall, this yields over 300,000 TRs across all subjects and stories, or ~5 days of fMRI data. All data and materials have been standardized and staged for public release. The stories span a variety of media, including commercially-produced radio and internet broadcasts, authors reading written works, professional storytellers performing in front of live audiences, and experimental subjects verbally recalling previous events. Alongside the stimuli, we provide time-stamped word-level transcripts created using a semi-supervised forced-alignment algorithm. MRI data have been organized according to the machine-readable Brain Imaging Data Structure (BIDS) with exhaustive metadata. Anonymized subject labels are linked across stories and include demographic and behavioral variables including age, gender, group or condition, and comprehension score (where available). MRI data are provided with various levels of preprocessing, including volumetric and surface-based spatial normalization, spatial smoothing, and temporal filtering with confound regressors. To more effectively aggregate data across subjects and stories, we developed a variant of hyperalignment that capitalizes on intersubject functional correlation (ISFC) analysis to derive a single connectivity-based shared response space across disjoint datasets. To validate the quality of the data, we applied intersubject correlation (ISC) analysis to each dataset. First, we measured ISCs in early auditory cortex to evaluate the temporal alignment of responses and identify outliers. Next, we performed whole-brain ISC analysis, revealing consistent responses throughout a network of cortical areas supporting language and event representation. Well-curated, naturalistic data have tremendous potential for re-use, and we hope the community will benefit from these data in disentangling the neural mechanisms of language comprehension.

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Nanosymposium

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Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.05

Topic: H.02. Human Cognition and Behavior

Title: Neural biomarkers of language proficiency in second language listeners

Authors: G. M. DI LIBERTO[1], J. NIE[2], J. YEATON[3], B. KHALIGHINEJAD[4], S. A. SHAMMA[5], ***N. MESGARANI**[2];
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Abstract: Speech comprehension requires our brain to process a variety of acoustic and linguistic elements. Recent research has found detailed insights on how, where, and when some of those properties are processed. However, there remains considerable uncertainty on how these mechanisms differ in the case of second-language learners. Here, we recorded electroencephalography (EEG) signals from native English (L1 group; N = 22) and native Chinese speakers (L2 group; N = 50) with varied English proficiency (poor to excellent) as they listened to English sentences. Behavioral measures of proficiency were derived by means of a standardized language test, which assigned each participant to a language level according to the Common European Framework of Reference for Languages (CEFR). Multivariate linear regression was used to quantify the coupling between EEG signals from each participant and the corresponding speech stimulus properties at the level of acoustics, phonemes, and semantics. This coupling allowed us to investigate the effect of language skills on the brain responses to speech at various processing levels. We found that cortical responses to speech differ between L1 and L2 listeners and change with the English proficiency level within the L2 group. The similarity of high-level cortical responses (semantic level) between L2 and L1 participants increased with language proficiency, while significant but more complex effects emerged for responses to lower-level properties of speech. Crucially, classifiers fitted on both low- and high-level cortical responses could correctly identify the proficiency of an L2 participant (low vs. high) with over 80% accuracy. We contend that the present finding provides a novel perspective on the cortical processing of a second-language and sets the basis for a novel procedure for objective measures of language proficiency from multivariate brain data.

Disclosures: N. Mesgarani: None. **G.M. Di Liberto:** None. **J. Nie:** None. **B. Khalighinejad:** None. **S.A. Shamma:** None. **J. Yeaton:** None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

Location: Room S402

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.06

Topic: H.02. Human Cognition and Behavior

Support: NIH/NIDCD 1F30DC017083
NIH/NIDCD 5U01NS098981
NIH/NIDCD 1R01DC014589

Title: Stitching cortical dynamics to reveal distributed network interactions for language production

Authors: *K. FORSETH[1], A. GIAHI SARAVANI[2], X. PITKOW[2], N. TANDON[3];
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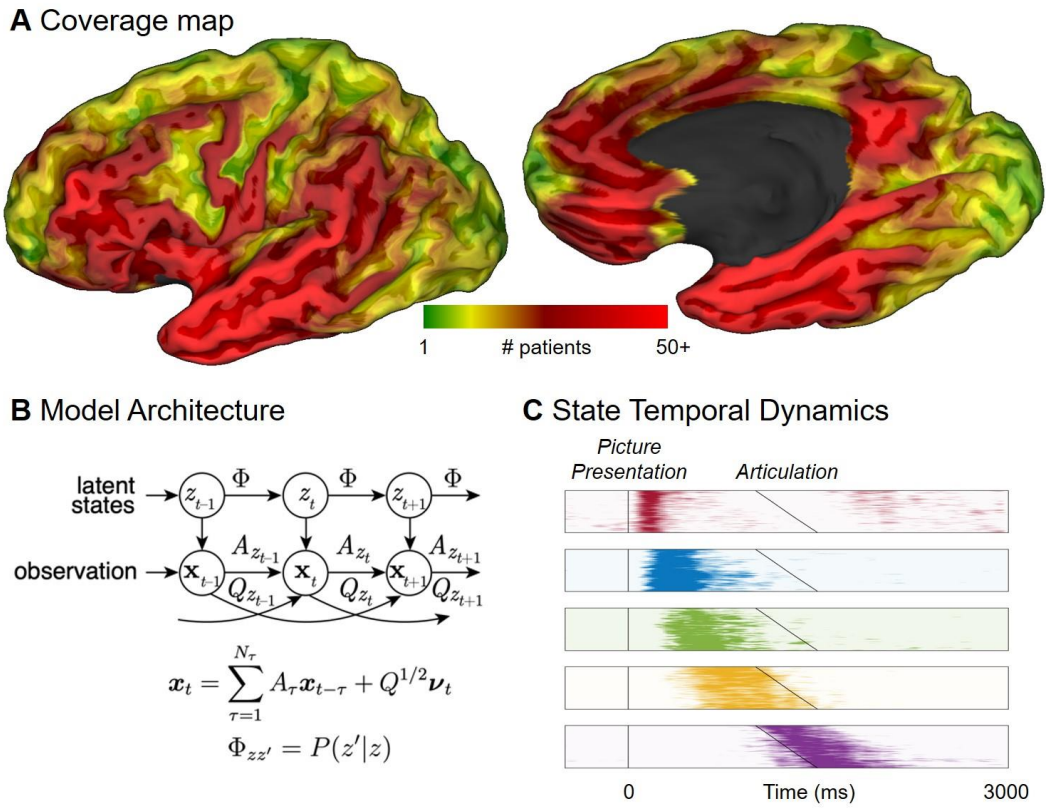
Abstract: Human speech production is an integrated multistage process. To understand the robust orchestration of distributed cortical networks for eloquent language function, it is essential to resolve the dynamic interactions between functionally distinct substrates. We use Autoregressive Hidden Markov Models (ARHMMs) on large-scale intracranial recordings of human cortex to reveal a consistent and interpretable evolution of neural states during overt speech production. Intracranial electrodes (n = 22,311; 129 patients), including both surface grid and depth electrodes, were implanted for evaluation of epilepsy. Importantly, these provided coverage over the entirety of the language dominant hemisphere with no brain region being sampled in fewer than 3 patients (Fig1A). Patients performed picture naming of common objects. 12 regions of interest - identified in previous analyses and distributed through all 5 cortical lobes - seeded network analysis with ARHMMs (Fig1B). We introduce a critical extension of the ARHMM architecture that accommodates incomplete network sampling in each patient to learn a conserved set of network dynamics using partially overlapping recordings sites across the cohort. ARHMMs explained the observed time series as a consequence of switching discrete hidden states, where each state is characterized by distinct stochastic linear dynamics. This principled probabilistic framework succeeded in resolving trial-by-trial state dynamics. We observed a consistent state sequence (Fig1C). Causal interactions between network nodes, quantified with pairwise partial direct coherence, revealed the progression of functional network motifs engaged between picture presentation and articulation (Fig1D). This framework has great potential to drive isolation and analysis of the network states that drive complex cognitive processes essential for an expansive set of human behaviors.



Disclosures: K. Forseth: None. **A. Giahi Saravani:** None. **X. Pitkow:** None. **N. Tandon:** None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

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Presentation Number: 111.07

Topic: H.02. Human Cognition and Behavior

Support: NIH/NIDCD 1F30DC017083
NIH/NIDCD 5U01NS098981
NIH/NIDCD 1R01DC014589

Title: Convergent cortical state dynamics in language networks for listening and reading

Authors: K. FORSETH, ***N. TANDON**;
UT Hlth. Sci. Ctr., Houston, TX

Abstract: People decode linguistic information from both orthographic and acoustic representations - written and spoken word, respectively - at high speed and fidelity. Here we investigate whether these parallel lead-in processes in early sensory cortex subsequently engage a shared lexical semantic network that supports naming. Intracranial electrodes (n=8619, 51 patients) were implanted for the electrocorticographic evaluation of epilepsy. These render the full spectrum of neural oscillations with excellent spatiotemporal resolution. To identify the lexical semantic network, we used a mixed-effects multilevel analysis of gamma (60-120 Hz) band power. The state dynamics of this network were subsequently resolved with an Autoregressive Hidden Markov Model. In two separate experiments, patients were asked to quickly and accurately articulate the name of common objects in response to short descriptions. The first experiment presented these stimuli as written words in rapid serial visual presentation; the second experiment presented spoken sentences. With the presentation of each written word, activity in the visual word form area was followed by engagement of the lexical (superior temporal sulcus and posterior middle temporal gyrus) and phonological (superior temporal gyrus) streams of reading. These loci were also engaged throughout the duration of the spoken stimuli. Importantly, the last word in each prompt was essential for binding the semantic concept (“*A person in charge of a courtroom”*). This triggered an identical lexical semantic network (middle fusiform gyrus, posterior middle temporal gyrus, intraparietal sulcus, and pars triangularis) prior to articulation. In a third experiment, patients were shown images of common objects which they named aloud. This engaged a lexical semantic network identical to that observed after reading and listening, except for the notable absence of posterior middle temporal gyrus. Juxtaposing the neural architectures that support the two predominant modalities of formalized language transmission informs our understanding of both specialized and shared cognitive language networks. This may generate insights for the rehabilitation of the substantial population affected by dyslexia or recovering from brain injury.

Disclosures: K. Forseth: None. **N. Tandon:** None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

Location: Room S402

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.08

Topic: H.02. Human Cognition and Behavior

Title: Functional mapping of language with high gamma electrocorticography

Authors: *J. SHUM, B. MAHMOOD, L. FANDA, P. C. DUGAN, D. FRIEDMAN, W. DOYLE, O. DEVINSKY, A. FLINKER;
NYU Comprehensive Epilepsy Ctr., New York, NY

Abstract: Electrical stimulation mapping (ESM) is the current gold standard for identifying eloquent language cortex which should be spared during epilepsy surgery. However, there are many limitations to this technique, particularly the risk of after discharges and seizures. ESM can also be time-consuming, requires excellent patient cooperation, and is not always well-tolerated by patients. High gamma electrocorticography (hgECoG) has been studied as another modality for pre-surgical language mapping as compared to ESM. HgECoG activity has been previously established as a robust marker of local cortical activity, making it an ideal candidate for functional mapping. However, existing studies comparing hgECoG to ESM have mixed results with highly variable sensitivities and specificities. It remains unclear what combination of hgECoG signal processing parameters and language tasks, as well as their spatial relationship, are most predictive of ESM results. To overcome these limitations we utilize a battery of five language tasks and a statistical modeling approach. Our language tasks capture multiple modalities of language processing and production and mirror the clinical paradigms employed during ESM. The tasks involved picture naming, visual word reading, auditory word repetition, auditory naming, and auditory sentence completion. Our statistical modeling approach utilizes a logistic regression model to predict which brain regions will be identified by ESM, and is based on hgECoG features during the five language tasks and normalized electrode spatial information. Using data from 8 subjects, our logistic regression model performed with an AUC of 0.81 and had a specificity of 0.94 and sensitivity of 0.41 at its optimal operating point. A 10-fold cross validation was preformed with an average AUC of 0.74 over the 10 models. Our model shows that high gamma ECoG is a clinically useful tool to complement stimulation based language mapping.

Disclosures: J. Shum: None. **B. Mahmood:** None. **L. Fanda:** None. **P.C. Dugan:** None. **D. Friedman:** None. **W. Doyle:** None. **O. Devinsky:** None. **A. Flinker:** None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

Location: Room S402

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.09

Topic: H.02. Human Cognition and Behavior

Title: Metaphoric language and brain plasticity

Authors: *M. ORKODASHVILI;
Vanderbilt Univ., Nashville, TN

Abstract: The present research looks into the influence of the so-called *higher order thinking* on the development of neuroplasticity in monolingual, bilingual and multilingual brains. *Higher order thinking* involves understanding of linguistic units and linguo-pragmatic means with non-literal meanings such as certain abstract notions (often of polysemantic nature), metaphors, and humor.
The research studies the effects of the recognition of abstract notions, metaphors, and humor in monolingual, bilingual and multilingual individuals on the development of their cognitive capacities.
The paper hypothesizes that transferring, explaining and understanding abstract notions, metaphors, and humor across languages is more difficult than transferring, explaining and understanding simple and concrete concepts or actions (e.g. concrete nouns and verbs denoting simple actions).
As a result of systematic mental exercise, subjects develop three important advantageous features of cognitive capacity: 1) quicker response time to understanding expressions and statements with non-literal meanings; 2) multitasking ability of understanding and reacting (or proacting) to simultaneous multiple tasks such as simultaneous translation and interpretation; and 3) quicker context anticipation. All three advantages indicate higher brain plasticity in the subjects under study.
The research tested the hypothesis by the method of analyzing response times and reading abilities in 20 monolingual, 20 bilingual and 20 multilingual individuals, as well as their reports of multitasking abilities.
The subjects were tested on understanding texts and expressions with non-literal metaphoric meanings.
The subjects had to read such expressions, understand them and explain or translate them to others.
The results showed that:
a) bilinguals and multilinguals were 85-95 milliseconds quicker in recognizing and understanding non-literal meanings as opposed to monolinguals;
b) monolinguals were 45-55 milliseconds quicker understanding complex texts after being exposed to the metaphoric expressions for a while;
c) subjects who had been exposed to metaphoric expressions and texts reported the ability of

performing two tasks at a time such as simultaneous translation in multiple languages more often than those who had not been exposed to such non-literal expressions;
d) furthermore, in the process of reading a new text, the subjects who had been exposed to metaphoric expressions, anticipated the subsequent words, actions or concepts from the context with 78 % precision, as compared to those who had not been exposed to such expressions and who revealed only 22 % precision of anticipation.

Disclosures: M. Orkodashvili: None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

Location: Room S402

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.10

Topic: H.02. Human Cognition and Behavior

Support: ANR
Vetenskapsradet

Title: Neural resources shared by language and tool-use: A basis for tool-use benefits over syntactic abilities

Authors: *S. THIBAULT[1,2,3], V. BOULENGER[4,5], A. ROY[4,5], C. BROZZOLI[1,2,3,6];
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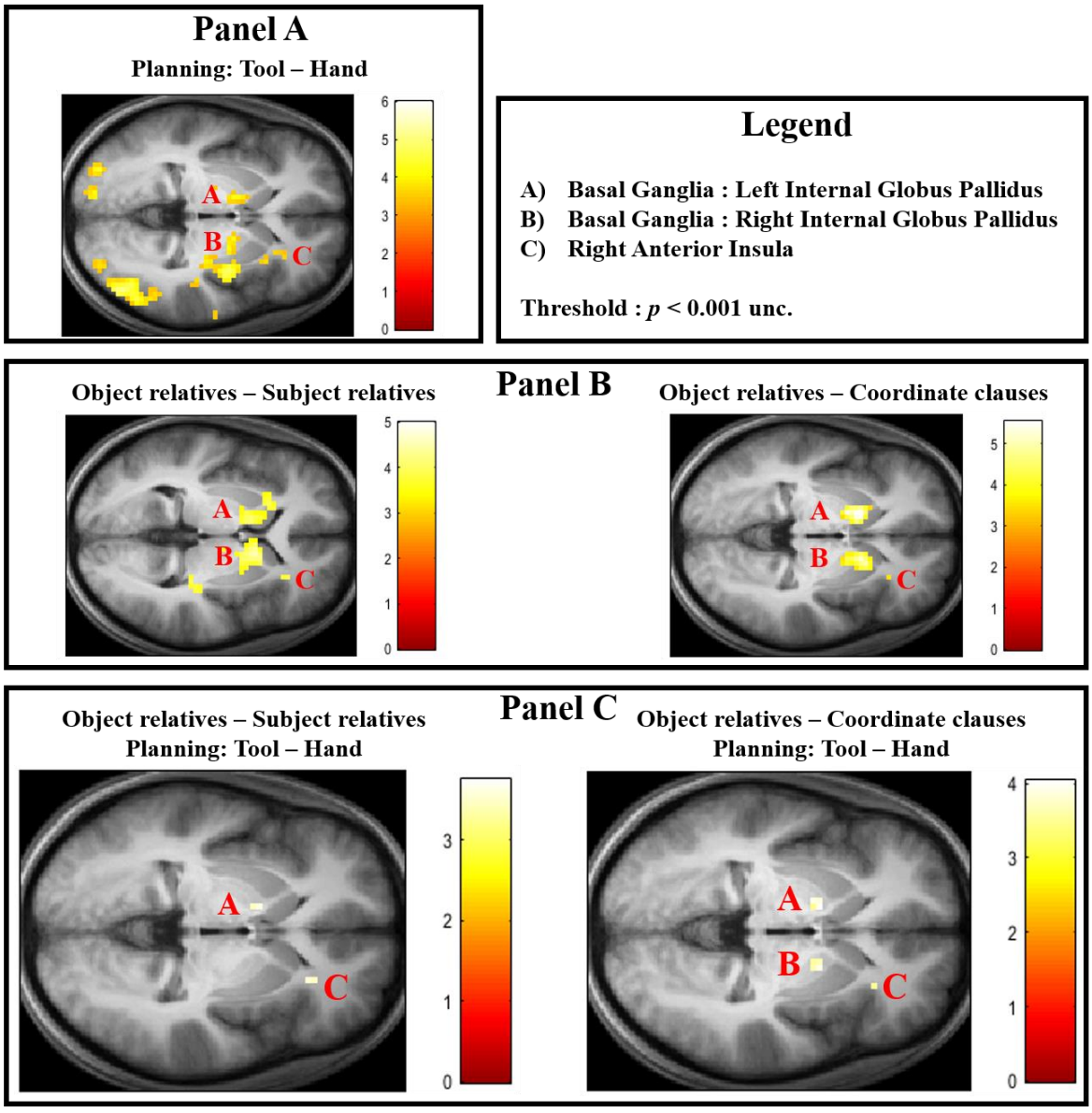
Abstract: Previous works have suggested a role for Basal Ganglia (BG) in syntactic processing, beside their involvement in temporal organization of motor sequencing in tool-use. The extent of this overlap and whether it is functionally relevant remain unknown. In two neuroimaging and behavioral studies, we investigated first the overlap between tool-use and syntax within the same participants and second, given the shared neural resources, whether tool-use training can impact syntax. Using fMRI, we assessed comprehension of complex relative clauses in 19 healthy adults. The same group also underwent a motor task, requiring to move a peg with a tool and the bare hand. We examined the specific tool-use network by contrasting tool to hand neural activity (Panel A). The syntactic network (B) was featured by contrasting activity for complex (i.e. object relatives) to simpler structures (i.e. subject relatives or coordinate clauses). Conjunction analysis showed significant overlap between tool-use planning and syntax neural networks (C). No overlap was found with the hand motor control network. The shared network involving BG and right anterior insula (raIns) might subserve similar functions for tool-use and syntax, such as handling complex hierarchical sequences, either motor or linguistic. In a behavioural experiment on 78 novel participants, we examined the impact of tool-use on syntax. Syntactic abilities were

assessed with the same task, before and after one of three possible training regimes. One group underwent tool-use training requiring to insert pegs on a board with a tool. Two control groups were either trained on the same task with the hand or instructed to watch a video. Mixed-model analysis showed significant improvement to process most complex clauses after tool-use for participants with initial higher syntactic abilities (p<0.001). Overall, these results reveal functional overlap between tool-use and syntax within BG and raIns, as well as enhanced syntactic abilities after tool-use training. This opens possibilities for beneficial transfer effects of tool-use over syntax.



Disclosures: **S. Thibault:** None. **V. Boulenger:** None. **A. Roy:** None. **C. Brozzoli:** None.

Nanosymposium

111. Language: Physiology, Plasticity, and Cognition

Location: Room S402

Time: Sunday, October 20, 2019, 8:00 AM - 10:45 AM

Presentation Number: 111.11

Topic: H.02. Human Cognition and Behavior

Support: CONICYT Grant Number 21151047
CONICYT Grant Number 1150241

Title: Visemic salience modulates mu suppression during silent speech perception: Preliminary evidence for the articuleme

Authors: *M. MICHON[1,2], G. N. BONCOMPTE[3], V. LÓPEZ[4];
[1]Pontificia Univ. Católica De Chile, Santiago, Chile; [2]Facultad de Psicología, Univ. Diego Portales, Santiago, Chile; [3]Univ. Catolica De Chile, Santiago, Chile; [4]Pontificia Univ. Católica de Chile, Santiago, Chile

Abstract: The involvement of motor cortices during auditory speech perception has been increasingly documented. Particularly, mirror neurons activity has been reported in EEG studies evidenced by the suppression of mu rhythms in central electrodes. In the frame of sensorimotor integration of speech, a fascinating question remains unanswered respect to visual speech perception. The current study aims to determinate if the processing of visual counterpart of phonemes (i.e., the visemes) activates motor regions. Thirty participants observe or imitate silent videos displaying a talking face either producing different syllables (stop consonant + vowel) or backward syllables (i.e., nonlinguistic orofacial movements). The syllables presented differed in their place of articulation (bilabial vs alveolar vs velar) and consequently in their visemic salience. The time-frequency dynamics of the EEG signal were analyzed and evidenced a significant suppression of mu rhythms during the perception of syllables compared to backward syllables. Interestingly, the suppression of mu rhythms was modulated by the visemic salience, the bilabial syllables eliciting more suppression than velar syllables. Moreover, when the orofacial effectors of the participants were restricted, the mu suppression found for bilabial syllables significantly diminished. Altogether, these results suggest that visual speech cues perceived without any auditory counterpart are represented in motor cortices and that the amount of this motoric representation depends on visual salience and on the availability of the perceiver's orofacial effectors. The results of the current study are discussed in the frame of an hypothesized trimodal model network where phonemes, visemes and *articulemes* (i.e., the vocal-motor sequence required to pronounce a phoneme) are mapped in a cross-modal repertoire.

Disclosures: M. Michon: None. **G.N. Boncompte:** None. **V. López:** None.

Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

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Presentation Number: 112.01

Topic: H.03. Schizophrenia

Support: NIH Grant MH057440

Title: Peripubertal treatment with mGluR2/3 agonist prevents dopamine system hyperactivity in adulthood in MAM model of schizophrenia

Authors: *S. SONNENSCHEIN, A. A. GRACE;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Pomaglumetad methionil (POM), a group 2 metabotropic glutamate receptor (mGluR2/3) agonist, showed promise as a novel antipsychotic in preclinical research but failed to show efficacy in clinical trials, though it has been suggested that it may be effective in certain patient populations. Although previous studies have shown that mGluR2/3 agonists have no effect on dopamine (DA) in normal rats, we used the methylzoxymethanol acetate (MAM) rat model of schizophrenia to determine whether POM may regulate DA neuron activity in a model representative of the hyperdopaminergic state thought to underlie psychosis, compared to control (SAL) rats. MAM and SAL rats were treated with POM (1, 3, 10 mg/kg, i.p) or 1 mg/kg saline 30 min prior to anesthetized in vivo electrophysiological recordings. VTA DA neuron activity was measured by passing an electrode in a grid-like pattern, counting the number of spontaneously firing DA neurons, and analyzing their firing rate and bursting activity. POM dose-dependently reduced the number of spontaneously active DA neurons in the VTA of MAM rats to control levels and the reduction persisted in MAM rats following 14d daily treatment (3 mg/kg). This effect was not observed in SAL rats following acute or repeated POM treatment. Intra-ventral hippocampal infusion of POM (0.5 µl; 1µg/µl) was sufficient to reduce DA neuron activity in MAM rats without affecting SAL rats. POM (1 and 3 mg/kg, i.p.) also increased novel object recognition (NOR) in MAM rats without affecting SAL rats. To determine whether peripubertal POM treatment may prevent the development of the MAM pathology, we treated MAM and SAL rats with POM (3 mg/kg, i.p.), saline (1 ml/kg), or no injection from postnatal day (PD) 31-40. Rats were tested for NOR and VTA DA neuron activity was recorded in either early adulthood (PD 47-53) or late adulthood (PD 83-90). MAM rats treated with POM demonstrated normalized DA neuron activity at both timepoints and increased NOR in late adulthood compared to no injection, though not compared to saline injection. These results suggest that POM indirectly regulates DA neuron activity by reducing increased ventral hippocampal activity and can prevent DA neuron hyperactivity in adult MAM rats following peripubertal administration.

Disclosures: S. Sonnenschein: None. **A.A. Grace:** None.

Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

Location: Room S401

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 112.02

Topic: H.03. Schizophrenia

Support: In-house funding University of Iowa

Title: Linking differential resting-state connectivity to spatial gene expression patterns in a mouse model of 22q11 deletion

Authors: *T. NICKL-JOCKSCHAT[1], N. GASS[2], Z. J. PETERSON[3], M. DIDRIKSEN[4], A. J. SCHWARZ[5], C. HAN[2], E. SCHWARZ[2], A. SARTORIUS[2], A. MEYER-LINDENBERG[2]; [1]Dept. of Psychiatry, Iowa Neurosci. Instit, Iowa City, IA; [2]Central Inst. of Mental Hlth., Mannheim, Germany; [3]Univ. of Iowa, Iowa City, IA; [4]H. Lundbeck A/S, Valby, Denmark; [5]Translational Res. and Early Clin. Develop., Takeda Pharmaceuticals, Cambridge, MA

Abstract: 22q11 deletion is commonly regarded as the strongest known single molecular genetic risk factor for developing schizophrenia (Van et al., 2017). Characterizing the effects of this CNV on neural networks offers a unique avenue towards delineating polygenic interactions in the pathogenesis of this disorder. We here relied on a mouse model of 22q11 deletion (Df(16)A+/-) and littermate controls to identify differential resting-state functional connectivity (rsFC) patterns across networks derived from six seed regions (N. accumbens, hippocampus, infralimbic, retrosplenial and orbitofrontal cortex, ventral tegmental area). Using the Allen Mouse Brain Atlas (Lein et al., 2007), we analyzed (Kumar et al., 2018) the expression patterns of the genes deleted in our model (27 genes in the deletion, 24 of them available in the Allen Mouse Brain Atlas) to identify which gene expression patterns spatially overlapped with differential connectivity (*hyper*- or *hypo*connectivity with the seed) in these six networks. To confirm the translational relevance of our findings in humans, we used machine learning to explore, whether genes implicated by our analyses were co-expressed in human tissues. We found significant associations between differential resting-state connectivity and spatial gene expression patterns for all contrasts. Genes overexpressed in a given region with differential connectivity formed functional networks above chance for all contrasts. These networks were functionally annotated with the terms “response to drug”, “axon part”, “plasma membrane” and “flavin adenine dinucleotide binding”. Of note, two genes, *COMT* and *Trmt2a*, were consistently overexpressed in all regions showing hyper- or hypoconnectivity with any of the six seeds. Our analyses of human data sets confirmed co-expression of *COMT* and *Trmt2a* in humans, but did not retrieve any different patterns between patients and controls. Our findings suggest that differential resting-state connectivity patterns in our mouse model of 22q del are mediated by polygenic networks in regions with altered connectivity. *COMT* and *Trmt2a* seem to play a key role in this regard and form the core components of these networks. Co-expression patterns in humans hint at a potential interaction also in humans. Although the mechanistic interactions between the two genes have not been explored yet, but might constitute an important link

between neurotransmission, transcriptional activity and functional changes on a neural systems level.

Disclosures: **T. Nickl-Jockschat:** None. **N. Gass:** None. **Z.J. Peterson:** None. **M. Didriksen:** A. Employment/Salary (full or part-time):; Lundbeck. **A.J. Schwarz:** A. Employment/Salary (full or part-time):; Takeda. **C. Han:** None. **E. Schwarz:** None. **A. Sartorius:** None. **A. Meyer-Lindenberg:** None.

Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

Location: Room S401

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Presentation Number: 112.03

Topic: H.03. Schizophrenia

Support: NIMH Grant F31 MH113403-02
Departmental Support USF Dept Molecular Medicine

Title: Altered behavior, neurogenesis, and $GABA_A$ receptor modulation in a Reln and Disc1 double-hit model for genetic susceptibility to schizophrenia

Authors: *H. L. MAHONEY[1], J. FAULKNER[2], B. CAPRARO[2], E. PETERSON[2], H. JUSTIN[2], D. GONZALEZ[2], J. J. GAMSBY[1], E. J. WEEBER[3], D. GULICK[1];
[1]Mol. Med., [3]Mol Pharmacol & Phys, [2]Univ. of South Florida, Tampa, FL

Abstract: This study evaluates a novel transgenic mouse model in which two putative schizophrenia (SCZ) susceptibility genes, Disrupted-in-schizophrenia-1 (DISC1) and Reelin, have been disrupted. Reelin is essential for proper brain lamination during development, and is a key regulator of neurogenesis and synaptic plasticity in the adult. Reelin is reduced by approximately 50% in human SCZ postmortem brain tissue. DISC1 is involved in multiple cellular processes was various binding partners, including adult neurogenesis, dendritogenesis, and $GABA_A$ receptor trafficking.
We hypothesized that combined genetic disruption would result in a more severe SCZ-like behavioral phenotype than either mutation alone, and that alterations in inhibitory signaling and neurogenesis would underlie this phenotype.
Heterozygous reeler mice were bred with mice expressing dominant-negative c-terminal truncated human DISC1 to produce offspring with both mutations. These mice were subjected to a battery of SCZ-relevant behavioral tests. To attempt to rescue anxiety-like behavior, mice were treated with diazepam and allowed to explore the open field. $GABA_A$ receptor subunit expression was assessed in tissue lysate from the prefrontal cortex (PFC) and hippocampus (HPC), and cytoplasmic and synaptosomal fractions of the cortex. Neurogenesis and neuronal maturation were assessed using doublecortin immunohistochemistry and stereological

estimation.
Compared to wild-type, double transgenic mice have reduced pre-pulse inhibition, indicating a sensorimotor gating deficit. In the open field, these mice spent more time immobile, and exhibited increased freezing and immobility in several other tests. Diazepam failed to rescue anxiety-like behaviors, instead increasing activity. We found reduced $GABA_A$ receptor subunit 5 in the PFC, HPC, and cortical synaptosomes, while subunit 1 was reduced in the HPC but increased in the PFC. Maturation of adult-born neurons was also altered in double transgenic mice. While there was no difference in the total number of doublecortin positive cells, more of these cells were in immature stages of development.
To our knowledge, this is the first study to combine homozygous DISC1 mutation with Reelin haploinsufficiency. The paradoxical reaction to diazepam suggests that these mice have altered $GABA_A$ receptor expression or subunit composition, an idea reinforced by our western blot results. Further study will focus on expanding our understanding of the changes in adult neurogenesis and inhibitory signaling. Following characterization, this model will be used to investigate gene-environment interactions that may lead to SCZ susceptibility.

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Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

Location: Room S401

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Presentation Number: 112.04

Topic: H.03. Schizophrenia

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)
Southwest National Primate Research Center, Pilot Program (VS1259)

Title: Development and characterization of a non-human primate model of maternal immune activation

Authors: *D. SANTANA-COELHO[1], J. O'CONNOR[1], D. LAYNE-COLON[2], S. TARDIF[2]; [1]Univ. of Texas Hlth. At San Antonio, San Antonio, TX; [2]Texas Biomed. Res. Inst., San Antonio, TX

Abstract: Fetal exposure to inflammation during pregnancy elevates the risk of neurodevelopmental disruption in the exposed offspring. Disorders such as autism have been linked to maternal infection and inflammation during pregnancy in humans. Although rodent models have been used extensively to model the developmental consequences of maternal immune activation, the extent to which the information acquired through there models can be

extrapolated to human development can be limited by the physiological differences between rodents and primates. In order to bridge this translational gap, we sought to establish the model of maternal immune activation through prenatal administration of polynosinic-polycyticylic acid-poly-L-lysine (Poly IC-LC) conjugate in marmosets (Callithrix jacchus). The size, developmental timeline and social nature of marmosets makes them an ideal non-human primate model. Pregnant marmoset were treated with Poly ICLC on gestational day 63, 65 and 67. Deficits in social communication, a core feature of autism, were tested using the isolation-induced vocalization test (at 2, 4 and 8 weeks of age), and an adapted version of the three chamber test commonly used in rodents was used to evaluate deficits in sociability in early adolescent offspring (3.5 month old offspring).

Disclosures: D. Santana-Coelho: None. **J. O'Connor:** None. **D. Layne-Colon:** None. **S. Tardif:** None.

Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

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Presentation Number: 112.05

Topic: H.03. Schizophrenia

Support: NIMH Grant R01 MH111177
NIA Grant R37 AG011230
Lycaki-Young Funds from the State of Michigan

Title: Reduced myelin content and smaller axons of key white matter tracts in schizophrenia: Evidence for structural dysconnection

Authors: *B. LU[1], S. PATEL[2], J. LOSIOWSKI[2], D. KHATIB[2], M. ARSHAD[2], N. RAZ[3], V. DIWADKAR[2], J. STANLEY[2];
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Abstract: While the exact etiology of schizophrenia remains unclear, alterations in myelin microstructure have been found among affected individuals. Detecting disruptions in the myelination process may contribute to understanding the neural dysconnectivity mechanisms underlying the neuropathology of schizophrenia. Here, we used multi-echo T_2 (ME-T_2) imaging for *in vivo* quantification of the myelin water fraction (MWF), reflecting myelin content, and geometric mean (geomT_{2IEW}) reflecting axonal size/packing density. ME-T_2 images from 36 DSM-V diagnosed schizophrenia patients (SZ; 25M + 11F; 28.8±6.0 years) and 41 healthy controls (HC; 19M + 22F; 28.7±6.2 years) were collected. MWF and geomT_{2IEW} values in seven white matter regions of interest [anterior and posterior limb of the internal capsule (ALIC and

PLIC), external capsule (EXC), genu and splenium of the corpus callosum (GENU and SPL), and superior longitudinal and inferior fronto-occipital fasciculi (SLF and IFOF)] were extracted. Group differences were tested using a repeated measures GEE framework with group, side, age, and sex as independent variables. Compared to HC, SZ demonstrated significantly lower MWF values in the ALIC, PLIC, EXC, SPL, and IFOF, and significantly lower geomT_{2IEW} values in the ALIC, EXC, GENU, SPL, and IFOF ($p < 0.04$). The group-by-age interaction was also significant for MWF values in the ALIC, EXC, and IFOF reflecting increased divergence with age ($p < 0.03$). These results demonstrate that multiple key tracts of SZ patients are characterized by reduced myelin content and smaller axonal size (lower geomT_{2IEW} values). Additionally, the differential age effect suggests an altered, neurodevelopmentally mediated progression in the myelin distribution of these patients. This is notable given that, in healthy development, both MWF and geomT_{2IEW} values increase with age (reflecting continued myelination of axons and increase in axonal size well into middle adulthood). These results, a) provide novel evidence of the dysconnection hypothesis in white matter tracts, b) are consistent with neurodevelopmental models of schizophrenia and c) suggest an anatomical correlate for functional and connectivity deficits found with functional MRI images. Further investigation is ongoing to associate these myelin-related alterations with the symptomatology commonly found in those living with schizophrenia.

Disclosures: **B. Lu:** None. **S. Patel:** None. **J. Losiowski:** None. **D. Khatib:** None. **M. Arshad:** None. **N. Raz:** None. **V. Diwadkar:** None. **J. Stanley:** None.

Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

Location: Room S401

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 112.06

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U54 EB020403
NIH Grant R01 MH117601

Title: Mapping combined genetic risk for bipolar disorder & schizophrenia to the human brain in UK Biobank

Authors: *L. DING, N. JAHANSHAD, P. THOMPSON;
Imaging Genet. Center, USC Mark and Mary Stevens Neuroimaging and Informatics Inst., Marina Del Rey, CA

Abstract: Schizophrenia (SCZ) and Bipolar disorder (BD) are psychiatric disorders with known overlap in clinical symptoms. Some studies have suggested an overlap in genetic susceptibility between the two (Smeland 2019). Here we examined the association between the combined

genetic risk profile for the two disorders and brain phenotypes across several cortical regions. 10,573 healthy UK Biobank subjects (age 44-79 yrs; 5507 female, 5066 male) with both genetic and brain imaging data were included in the analysis. T1-weighted brain MRI scans were processed using FreeSurfer v5.3 and the ENIGMA pipeline. Surface area (SA) and thickness (TH) in 68 cortical regions were evaluated . Each subject's polygenic risk score (PRS) was calculated as a weighted sum of the risk variants across the genome with associated *p*-value less than a threshold pT. Each variant's weight is determined from the association statistics (log-odds ratio) of an independent GWAS study. 14 PRS scores were generated for each individual, reflecting increasing cut-offs for pT from 10^{-5} to 1. GWAS summary data provided by the Psychiatric Genomics Consortium (PGC) was used to determine these weights (BD and SCZ Working Group of the PGC, 2018). This GWAS analysis collapsed BD & SCZ into a single phenotype outcome and ran GWAS on a cohort with the combined sample of 53,555 BD & SCZ patients considered as cases with 54,065 controls. Of all the SNPs present in the summary data, only the index SNP showing the strongest evidence for association within each 500 kb LD block of SNPs was used for PRS calculation. Using a *p*-value cut-off of pT <= 0.3, we identified 11 brain regions that were negatively associated with PRS_{BDSCZ} after controlling for false discovery rate at $\alpha = 0.05$ level using the Benjamini-Hochberg procedure, accounting for age, sex, intracranial volume and the first 4 ancestry components calculated using multi-dimensional scaling; regions included the entorhinal cortex surface area and the medial orbitofrontal cortex, which show differences in both BD and SCZ patients compared to controls (van Erp et al., 2018, Hibar et al., 2017). Higher PRS_{BDSCZ} was associated with smaller surface area or thickness in all the identified regions. We also examined global SA and mean TH: both were negatively associated with PRS_{BDSCZ} at threshold pT <= 0.3 (p_{SA}=0.015 , P_{TH} =0.034) after adjusting for the same covariates mentioned above. Our results suggest that, within the general population, the combined genetic risk for BD and SCZ is associated with morphological alterations in brain regions known to be disrupted in these disorders.

Disclosures: L. Ding: None. **N. Jahanshad:** Other; NJ is MPI of a research related grant from Biogen, Inc for work unrelated to the contents of this manuscript. **P. Thompson:** Other; PT is MPI of a research related grant from Biogen, Inc for work unrelated to the contents of this manuscript..

Nanosymposium

112. Modeling of Schizophrenia Relevant Risk Factors

Location: Room S401

Time: Sunday, October 20, 2019, 8:00 AM - 9:45 AM

Presentation Number: 112.07

Topic: G.08. Drugs of Abuse and Addiction

Support: Grant 60564 from the John Templeton Foundation

Title: Chronic paternal THC in rats prior to mating causes long-lasting behavioral disruption in their offspring

Authors: *E. D. LEVIN, Z. HOLLOWAY, A. B. HAWKEY, E. PIPPEN, H. WHITE, B. KENOU, J. KIM, E. GREENGROVE, A. H. REZVANI, S. MURPHY;
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Abstract: As cannabis becomes legalized, risks of cannabis and THC on neurodevelopment need to be understood. Abundant research has characterized risks of maternal exposure for producing adverse neurobehavioral effects in the offspring. However, comparatively little is known about the risks engendered by paternal exposure to cannabis or THC prior to conception. We have previously shown that preconception delta-9-tetrohydrocannabinol (THC) exposure in male rats significantly alters sperm DNA methylation. We also found altered sperm DNA methylation in human males who smoke cannabis. The current study investigated the intergeneration effects of chronic THC exposure of young adult male Sprague-Dawley rats (0, 2 or 4 mg/kg/day SC for 28 days) prior to mating with drug naïve female rats. This paternal THC exposure did not significantly impact the clinical health of the offspring. However, the offspring of THC exposed fathers did show significant alterations of behavioral function. Paternal THC exposure caused significant locomotor hyperactivity in adolescent offspring and significant cognitive dysfunction when they became adults. Specifically, during adolescence there was significant locomotor hyperactivity in the offspring of fathers exposed to 2 mg/kg/day of THC prior to mating. This hyperactivity diminished as the animals matured. There were cognitive effects of paternal THC exposure as well. During the novel object recognition task, the controls maintained their relative preference for the novel object across the duration of the ten-min session while the rats whose fathers received THC (2 mg/kg/day) showed a significantly greater drop-off in interest in the novel object during the second half of the session. In the 16-arm radial maze, the 4 mg/kg/day paternal THC dose caused a significant delay in learning. This study found that that paternal THC exposure before conception can cause detrimental behavioral effects in the offspring, including locomotor hyperactivity, and cognitive impairment. Future studies are needed to investigate the underlying mechanisms driving these aberrant developmental outcomes and seek to identify possible behavioral or pharmacological treatments.
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Disclosures: E.D. Levin: None. **Z. Holloway:** None. **A.B. Hawkey:** None. **E. Pippen:** None. **H. White:** None. **B. Kenou:** None. **J. Kim:** None. **E. Greengrove:** None. **A.H. Rezvani:** None. **S. Murphy:** None.

Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 185.01

Topic: A.05. Axon and Dendrite Development

Support: NIH R01 MH114102
NIH R01 NS097161

Title: Mechanisms of Robo3 activation in the developing spinal cord

Authors: *J. PAK[1], J. WANG[1], Z. DELOUGHERY[3], Y. PARK[2], A. JAWORSKI[4], E. OZKAN[1];
[1]Biochem. and Mol. Biol., [2]Human Genet., Univ. of Chicago, Chicago, IL; [3]Mol. Pharmacol. and Physiol., [4]Neurosci., Brown Univ., Providence, RI

Abstract: Axon pathfinding requires careful coordination of receptor signaling on neuronal growth cones through activation by extracellular guidance cues. In the developing spinal cord, Roundabout (Robo) family proteins act as receptors that mediate the repulsive response of migrating axons. While the midline secreted Slit is known to be the canonical ligand for Robo1 and Robo2, Robo3 has been shown instead to mediate a repulsive response in the presence of another ligand, NELL2. We recently determined the three-dimensional structure of NELL2 bound to Robo3 to reveal the molecular interface for complex formation; however, we have yet to elucidate the molecular mechanisms that regulate Robo3 signaling upon NELL2 binding. Here, we present biochemical, biophysical, and structural data that demonstrate the conformational and stoichiometric changes that Robo3 undergoes in response to NELL2 binding. Our previous studies have shown that the second and third epidermal growth factor-like (EGF) domains of NELL2 bind to the first Fibronectin type III (FN) domains of Robo3. Surprisingly, we have also identified through surface plasmon resonance (SPR) that Robo1 FN1-3 does binds to NELL2 EGF1-6, while the full Robo1 ectodomain (ECD) demonstrates reduced binding affinity with NELL2. This change in binding affinity in Robo1 is likely due to steric occlusion of the NELL2 binding site. Indeed, we show through small angle x-ray scattering (SAXS), multi-angle light scattering (MALS), and analytical ultracentrifugation (AUC) that Robo3 takes the form of a fully extended protein and is a monomer in solution, as opposed to Robo1/2 which have been demonstrated to take the form of a compact dimer. Lastly, we demonstrate that Robo3 and NELL2 are capable of forming clusters likely through multiple binding sites. This higher-order complex formation is dependent on the trimerization of NELL2 through its coiled-coil domain. Together, these data provide a possible model of Robo3 signaling, along with the possibility of coordinated signaling of Robo1/2 and Robo3 mediated by NELL.

Disclosures: J. Pak: None. **J. Wang:** None. **Z. Deloughery:** None. **A. Jaworski:** None. **E. Ozkan:** None. **Y. Park:** None.

Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 185.02

Topic: A.05. Axon and Dendrite Development

Support: NIH Director's Pioneer Award DP1 NS106665
The Dears Foundation Inc.

Title: Molecular controls over corticospinal neuron axonal branching at specific spinal segments

Authors: *Y. ITOH, V. SAHNI, S. J. SHNIDER, J. D. MACKLIS;
Harvard Univ., Cambridge, MA

Abstract: Corticospinal neurons (CSN, and related cortico-brainstem neurons; together "CSN") are located in layer V of the neocortex, and make synaptic connections with circuitry in the spinal cord and brainstem. CSN axons form the corticospinal tract (CST), the major motor output pathway from the cerebral cortex, essential for voluntary motor control. CSN are also clinically important. CSN degeneration in amyotrophic lateral sclerosis (ALS), along with degeneration of spinal motor neurons, causes spasticity and paralysis. In humans, damage to the CST following spinal cord injury is the principal cause of loss of voluntary motor control. Previous studies in our lab have identified combinatorial molecular controls over the specification and differentiation of CSN.

CSN exhibit striking anatomical and functional diversity: some CSN extend axons to targets in the brainstem and cervical spinal cord (i.e. bulbar-cervical targets; referred to here as CSN_{BC}), while others extend axons to thoraco-lumbar segments (CSN_{TL}). CSN_{BC} control face and arm movement, while CSN_{TL} control trunk and hindlimb movement. CSN in rostrolateral sensorimotor area are exclusively CSN_{BC}. In contrast, there exist projections to both bulbar-cervical and thoraco-lumbar spinal cord from CSN in medial sensorimotor cortex from early development into maturity (i.e. both CSN_{BC} and CSN_{TL}). We have identified that these anatomically distinct subpopulations are molecularly distinct, which has enabled us to develop molecular and intersectional viral labeling approaches to specifically delineate, and prospectively identify, segmentally distinct CSN subpopulations from development into maturity. Using these approaches, we are investigating CSN subpopulation-specific axonal projection and spinal segmental connectivity. For instance, we genetically labeled CSN_{TL} using a Cre-ER knock-in strategy, and identified that their mature axons develop gray matter innervation at all spinal segmental levels. Further, we identified a secreted proteoglycan expressed specifically by a subset of CSN_{BC} that non-cell-autonomously limits the axonal collateral branching from other CSN subpopulation in the cervical spinal cord. These results identify anatomical and molecular diversity among CSN, and molecular controls over their differential innervation in the spinal gray matter, as well as a novel mode of control over development of segmentally-, and likely functionally-specific circuit connectivity.

Disclosures: Y. Itoh: None. **V. Sahni:** None. **S.J. Shnider:** None. **J.D. Macklis:** None.

Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 185.03

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH/NIMHU01MH114825

Title: Early emergence of columnar synaptic circuit in human

Authors: *L. ZHOU, A. KRIEGSTEIN;
Eli and Edy The Broad Ctr. of Regeneration Med. and Stem Cell Res., Univ. of California - SF, San Francisco, CA

Abstract: The human brain is as complex as the universe and itself is the best “animal model”. The cortical column, which is one of the major characteristics of the cortex, provides an important and simplified entry to understand the complexity of the brain. However, how the human cortical column develops remains to be elusive. We thus focus on human tissue to explore the principles underlying early local circuit components by multidisciplinary strategies, including organotypic tissue culture, multiple viral tools, time-lapse imaging, calcium imaging, electrophysiological recordings, and multiplex fluorescence imaging. For the first time, we found that synaptically connected neurons form a columnar structure by genetically modified rabies in the early human brain (2nd trimester). Within the columns, most of connected cells were immature excitatory neurons, which developed from both stationary and migrating neurons. Synchronous calcium activity happens among the synaptically connected neurons, which may stabilize and maintain the columnar structure to adulthood in an activity-dependent way. Understanding the basic principles of human early circuit elements involving in cortical column formation will provide important hints for the causes and treatments of human neurodevelopmental disorders.

Disclosures: L. Zhou: Other; Contract-based consultant for Neurona Theraputics. **A. Kriegstein:** F. Consulting Fees (e.g., advisory boards); Neurona Theraputics.

Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 185.04

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NINDS T32NS048004

G. Harold and Leila Y. Mathers Foundation
HHMI

Title: Modular transcriptional programs define neuron subtype-specific connectivity

Authors: *J. YOO[1], Y. Z. KURMANGALIYEV[2], S. L. LOCASCIO[2], S. L. ZIPURSKY[2]; [1]UCLA, Los Angeles, CA; [2]UCLA/HHMI, Los Angeles, CA

Abstract: Neurons forming appropriate synaptic connections and wiring patterns during development is fundamental to building complex nervous systems. A promising approach to identify the genetic programs of neuronal wiring is to determine the transcriptome of neurons. Recent advances in single-cell sequencing have revealed a vast transcriptional diversity of neurons. A challenge is that various neuronal differences, ranging from morphology to functional synaptic activity, obscure the direct relationship between the transcriptome and neuronal connectivity.
Direction-selective T4/T5 neurons of the Drosophila visual system provide a unique opportunity to elucidate the linkage between the transcriptional control and neuronal connectivity. T4/T5 subtypes are closely related and morphologically well characterized. T4s and T5s each have four subtypes (T4a-d, T5a-d), whose axons target one of four layers in the lobula plate (a-d). T4 dendrites are located in medulla, and T5 dendrites are in lobula. Thus, four axon types (a-d) and two dendrite types (medulla or lobula) make eight different subtypes of T4/T5s.
We used single-cell RNA sequencing to profile the transcriptomes of developing T4/T5 subtypes during neurite targeting. Remarkably, we found that each subtype is not readily defined by unique molecular markers. Rather, transcriptional heterogeneity was represented by small sets of differentially expressed genes including transcription factors and cell surface molecules that were expressed in subtypes with shared neurite wiring patterns.
Taken together, our result suggests that transcriptional modules that define specific wiring patterns are assembled in different combinations to regulate subtype-specific connectivity. Repeated use of modular genetic programs may represent a common strategy for expanding neuronal diversity across complex nervous systems.

Disclosures: J. Yoo: None. **Y.Z. Kurmangaliyev:** None. **S.L. LoCascio:** None. **S.L. Zipursky:** None.

Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 185.05

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01 NS097161

Title: Molecular basis of synaptic specificity by a class of immunoglobulin superfamily receptors conserved across bilaterians

Authors: S. CHENG[1], Y. PARK[2], J. ASHLEY[3], J. W. THORNTON[2], R. A. CARRILLO[3], ***E. OZKAN**[4];
[1]Biochem. and Mol. Biol., The Univ. of Chicago, Chicago, IL; [2]Dept of Human Genet., [3]Mol. Genet. and Cell Biol., [4]Biochem. and Mol. Biol., Univ. of Chicago, Chicago, IL

Abstract: Synaptic connectivity is controlled by cell surface receptors, which can serve to assign unique identities to neuronal classes and physically mediate intercellular interactions. We recently identified a group of 32 immunoglobulin superfamily (IgSF) cell surface receptors, Dprs and DIPs, in the fruit fly, and demonstrated that molecular complexes can be formed by highly selective Dpr-DIP pairs. Furthermore, our group and others have now shown that Dprs and DIPs are expressed in a combinatorial fashion in many neuronal classes in the optic lobe, the ventral nerve chord, olfactory sensory neurons and the neuromuscular system, and are involved in neuronal functions, where they control synaptic specificity, synaptic development, axon fasciculation, and neuronal survival. In this study, we have determined three-dimensional crystal structures of five Dpr-DIP and DIP-DIP complexes, revealing molecular determinants of specificity and strategies for engineering of specific Dprs and DIPs. To demonstrate the power of structure-based protein engineering to study wiring, we have generated mutants of Dpr10 and its cognate DIP-alpha that specifically break homophilic or heterophilic interactions. We show that these mutants have phenotypes that are compatible with synaptic specification of the neuromuscular circuit in flies by the Dpr10-DIP-alpha intercellular complex. Furthermore, we reveal through phylogenetic analysis that molecular specificity of Dprs and DIPs can be traced based on their evolutionary histories. Finally, we establish IgLONs as orthologs to Dprs and DIPs in vertebrates, and show that other distantly related metazoan protein families, such as Kirrels can be similarly engineered to reveal wiring-related functions for IgSF-type neuronal cell surface receptors.

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Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 185.06

Topic: A.05. Axon and Dendrite Development

Support: NIH/NINDS R01 NS069861
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NJCBIR CBIR16IRG017

NJCBIR CBIR11FEL003

Title: Unsupervised clustering identifies morphometric features distinguishing dentate semilunar granule cells from granule cells through postnatal development

Authors: *A. GUPTA[1], A. PRODDUTUR[2], Y.-J. CHANG[3], J. GUEVARRA-FERNÁNDEZ[4], V. SANTHAKUMAR[5];
[2]NEUROLOGY AND NEUROSCIENCES, [1]Univ. of California, Riverside, CA; [3]The Rutgers Univ., Newark, NJ; [4]Rutgers NJMS, Newark, NJ; [5]Pharmacology, Physiol. & Neurosci., New Jersey Med. Sch. Dept. of Pharmacol. and Physiol., Newark, NJ

Abstract: Semilunar Granule Cells (SGCs) have been proposed as a morpho-functionally distinct class of hippocampal dentate projection neurons contributing to feedback inhibition and memory processing. However, whether SGCs retain their unique structural characteristics through postnatal development remains unresolved. Focusing on postnatal days 11-13, 28-42 and +120, corresponding with infancy, adolescence, and adulthood, we examined whether SGCs differ from granule cells (GCs) in somatodendritic morphology. Cell morphologies of putative SGCs and GCs were reconstructed in 3D (Neurolucida 360) from neurons filled with biocytin during whole cell recordings in hippocampal slices from rats aged 11-150 days and processed post hoc for biocytin immunostaining. SGCs and GCs were identified based on axons entering hilus, molecular layer dendrites with spines and somata in the inner molecular or granule cell layer respectively. Algorithms in Neurolucida Explorer (MBF Biosciences) were used to extract 42 distinct somatodendritic morphological parameters from 35 neurons and analyzed by unsupervised hierarchical clustering, and principal component analysis (PCA), using R packages including Cluster, FactoMineR. The PCA analysis indicated that the first 5 dimensions, retained over 77% of the variance in the entire dataset, thus included in the subsequent variable analysis. Testing on the basis of investigator-assigned classification identified that grouping based on cell-type segregated into two partially overlapping clusters, while grouping based on animal age showed considerable overlap suggesting that morphologically based clustering segregated by cell type rather than age. Unsupervised hierarchical clustering on morphometry identified 2 major clusters one including 9 putative GCs and one SGC and the second with 18 putative SGCs and 7 GCs. The top 5 morphological variables which best represent the principal components included the number of primary dendrites, second and third order dendritic segments, second order nodes and soma width. In analysis conducted based on investigator assigned classification, these parameters were significantly different between SGCs and GCs samples and failed to show age related changes (TW-ANOVA). In contrast, certain summed dendritic parameters including total numbers of dendritic segments, total nodes, total terminals and dendritic tortuosity showed neither cell-type nor age related differences. These findings highlight the distinct morphology of SGCs through development and identify the key dendritic features that distinguish SGCs from GCs regardless of developmental stage.

Disclosures: **A. Gupta:** None. **A. Proddutur:** None. **Y. Chang:** None. **J. Guevarra-Fernández:** None. **V. Santhakumar:** None.

Nanosymposium

185. Molecular Mechanisms of Synaptogenesis and Connectivity

Location: Room S405

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Presentation Number: 185.07

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NHMRC Project Grant APP1144145
ANU Futures Scheme Grant

Title: Molecular control of the cholinergic interneuron activity in the developing striatum

Authors: Y. RANJBAR-SLAMLOO, N. AHMED, L. GAO, S. AL ABED, Y. SONTANI, A. RCOM-H'CHEO-GAUTHIER, E. ARABZADEH, ***N. DEHORTER**;
The Australian Natl. Univ., Canberra, Australia

Abstract: Activity of the cholinergic interneurons (CINs) in the striatum is key for motor control, learning and habit formation. Yet the molecular mechanisms controlling the integration and the activity of CINs during development are largely unknown. Here, we investigated the role of the Er81 transcription factor as a potential regulator of CIN function. We found that Er81 is expressed in most of the CINs of the striatum at post-natal day 6 (P6) and downregulated at P30 in mice. Selective ablation of Er81 expression in CINs led to significant changes in the molecular identity and function of these interneurons. *In vitro* patch-clamp recordings at P30 revealed enhanced inward and delayed rectifier potassium currents, which are major regulators of tonic and phasic activity of CINs. Furthermore, we observed that striatal CIN morphology and connectivity are altered following Er81 deletion. Using *in vivo* multi-electrode array recordings in awake mice, we observed an overall decrease in spontaneous activity but enhanced sensory-evoked phasic responses in the specific absence of Er81 in CINs. Finally, behavioural analysis revealed that Er81-deficient adult mice exhibited significantly more flexibility and altered habit formation than control littermates. Our study unveils a fundamental mechanism of regulation of cholinergic cell development that impacts on adult striatal function.

Disclosures: Y. Ranjbar-Slamloo: None. **N. Ahmed:** None. **L. Gao:** None. **S. Al Abed:** None. **Y. Sontani:** None. **A. Rcom-H'cheo-Gauthier:** None. **E. Arabzadeh:** None. **N. Dehorter:** None.

Nanosymposium

186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

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Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 186.01

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: P20 GM103650 NIH NIGMS

Title: Experience-dependent maturation of inhibitory neuron connectivity in the dentate gyrus

Authors: *T. FENG[1], C. ALICEA[2], S. PIERAUT[3];
[1]Dept. of Biol., Univ. of Nevada Reno, Reno, NV; [2]Dept. of Biol., [3]Biol., Univ. of Nevada, Reno, Reno, NV

Abstract: Synaptic assembly and neural circuit development are strongly governed by experience during the postnatal period. Mice raised in an enriched environment (EE) from birth to juvenile time; e.g. pre-weaning enrichment (PE), have precocious maturation of their synaptic network, early onset of behaviors, and advanced sensory performance. While it has been well established that experience-dependent mechanisms shape both inhibitory and excitatory networks, the extent to which connectivity of distinct classes of GABAergic neurons is regulated by experience is unclear. In the dentate gyrus (DG), each inhibitory cell type projects axons to distinct laminae where they target specific subdomains along the somatodendritic axis of principal excitatory granular cells (GCs). This laminar organization is ideal to quantify distinct populations of inhibitory synapses using well-established synaptic markers. Taking advantage of this model, we investigated synaptic assembly of the major classes of interneurons in mice exposed to PE, and compared our findings to mice raised in standard housing (SH). We first confirmed that PE affected the development of inhibitory synapses in the DG using whole-cell patch clamp recording in acute slice. The frequency of miniature inhibitory and excitatory currents recorded on GCs were increased in PE compared to SH mice. To dissect the origin of this synaptic plasticity, we performed synaptic quantification using an immunofluorescent approach. Our quantifications revealed that the number of synapses formed by cholecystokinin-expressing (CCK) neurons is increased by 40% in PE mice. We also found a minor, yet significant, increase of inhibitory synapses localized in the molecular layer of the DG where somatostatin-expressing neurons contact GC dendrites. Interestingly, synapses formed by parvalbumin-expressing as well as calretinin-expressing interneurons were not affected. Finally, we tested whether the main excitatory inputs in the DG, formed by projection entorhinal cortical neurons, have an instructive role in the assembly of the inhibitory synaptic network. To this end, we manipulated neural activity using a chemogenetic approach and found that chronic inhibition of these afferents by h4MD induced a significant reduction of the CCK synapses in the DG. Altogether our results demonstrate that sensory experience shapes specific type of GABAergic synapses in the DG and this selective structural plasticity is, at least in part, controlled by cortical activity.

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Nanosymposium

186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

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Presentation Number: 186.02

Topic: A.06. Synaptogenesis and Activity-Dependent Development

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NIH Grant EY02858
The Champalimaud Foundation
The Good Ventures Foundation

Title: Neuronal non-classical MHCI Qa-1 is a novel receptor of activity-dependent plasticity via an innate immune receptor

Authors: *I. A. MARIN[1], A. Y. WEI[1], K. S. CHEW[1], A. D. BRADFIELD[2], C. J. SHATZ[1]; [1]Biol., [2]Stanford Univ., Stanford, CA

Abstract: The brain develops with an exuberant number of connections that are gradually pruned with use. This pruning is dependent on neuronal activity and is crucial during developmental critical periods. Previously we discovered a new role for major histocompatibility complex class I (MHCI) molecules in activity-mediated refinement of neural circuits. Initially thought to function solely in the immune system, recent work has revealed that MHCI proteins are expressed in the healthy brain, both in mice and humans. To date, the neuronal function of just two classical MHCI molecules (H2-K^b and H2-D^b), out of more than 50 family members, have been studied, demonstrating key roles in synaptic pruning and plasticity (Lee et al Nature 2014). Here we investigate the function of a novel non-classical MHCI: Qa-1, homologous to human HLA-E. In the immune system, Qa-1 is known to present antigens to NK and T cells, but its expression and function in healthy brain have been completely unexplored until now. We find that Qa-1 is expressed by over 70% of pyramidal neurons in layer 6 (L6) of cerebral cortex, and levels are regulated by visually-driven activity. Using ocular dominance plasticity (ODP) as a paradigm for activity-dependent circuit plasticity, we found in Qa-1 KO mice that strengthening of the open eye is greater than WT, following monocular eye closure during the visual cortical critical period. This and other phenotypes suggest that Qa-1 acts as a break on synaptic plasticity. The CD94-NKG2A/C/E family are known Qa-1 receptors in the immune system, and we report that they are expressed in cerebral cortex in glial cells. ODP is also enhanced in the visual cortex of mice carrying a mutation in Qa-1 that prevents binding to CD94-NKG2A/C/E receptors. Together, these results indicate a functional role for this ligand-receptor interaction in synaptic plasticity. Moreover, results expand understanding of MHCI function in the healthy brain, and point towards a novel and unexpected function for a non-classical MHCI expressed in CNS neurons interacting with a cognate receptor expressed in glia.

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Nanosymposium

186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

Location: Room S401

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 186.03

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Neuroligin-3 localizes to distinct synapse types via brain-region-specific phosphorylation

Authors: L. P. TUFFY[1], B. ALTAS[2], A. PATRIZI[3], K. DIMOVA[4], T. SOYKAN[5], M. C. AMBROZKIEWICZ[1], O. YAGENSKY[6], D. KRUEGER[7], M. HAMMER[1], H.-H. HSIAO[6], M. SASSOÈ-POGNETTO[8], J. J. E. CHUA[6], H. URLAUB[6], O. JAHN[1], N. BROSE[1], ***A. POULOPOULOS**[2];
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Abstract: Neuroligins (NLs) are postsynaptic adhesion proteins critical to the development and function of synapses in the brain. NLs regulate synapse assembly and transmission via interactions with presynaptic adhesion and postsynaptic scaffolding proteins. Each of the four NLs localizes to specific subsets of synapses, and their loss causes synaptic phenotypes with corresponding specificities. In mice, NL1 functions at excitatory synapses, while NL2 and NL4 function most prominently at inhibitory synapses. The localization and broad specificities of NL3, mutations of which cause autism in humans and autism-like behavior in mice, remain poorly understood. We investigated the synapse-type localization of NL3 across brain areas, and identified a molecular mechanism that differentially regulates synapse specificity of NL3. NL3 localizes to subsets of excitatory synapses in cortical regions, including hippocampus and cerebral cortex, while it localizes to inhibitory synapses in subcortical regions, including striatum, thalamus, and brainstem. We identified selective phosphorylation of NL3 in cortical areas that negatively regulates association of NL3 with Gephyrin and the inhibitory postsynaptic scaffold. These data reveal a broad pattern and an underlying mechanism for the synapse-type specificity of NL3, which may help interpret the different NL3-deletion phenotypes previously observed at distinct synapses, and contribute to understanding the synaptic etiopathologies of autism.

Disclosures: L.P. Tuffy: None. **B. Altas:** None. **A. Patrizi:** None. **K. Dimova:** None. **T. Soykan:** None. **M.C. Ambrozkiewicz:** None. **O. Yagensky:** None. **D. Krueger:** None. **M. Hammer:** None. **H. Hsiao:** None. **M. Sassoè-Pognetto:** None. **J.J.E. Chua:** None. **H. Urlaub:** None. **O. Jahn:** None. **N. Brose:** None. **A. Poulopoulos:** None.

Nanosymposium

186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

Location: Room S401

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 186.04

Topic: B.05. Neurotransmitter Release

Support: NIH Grant MH052804

Title: Neurexins play a central role in organizing presynaptic active zones

Authors: *F. LUO[1,2], A. SCLIP[1], M. JIANG[1], T. C. SUDHOF[1];
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Abstract: To achieve high-speed and precision neurotransmission, neurons assemble synapses with highly organized presynaptic and postsynaptic apparatus that are tightly registered by synaptic adhesion molecules. Neurexins are presynaptic cell-adhesion molecules that play crucial roles in many aspects of synapse formation and function. However, the exact roles of neurexins in fine-tuning presynaptic active zone functional organization remain much unknown. Taking advantage of the calyx of Held synapse as a model system in combination with the triple neurexin1/2/3 conditional knockout (TKO) mice, we performed systematic analyses of active zone function before and after ablation of all neurexins. We found that pan-neurexin deletion remarkably reduces synaptic strength by selectively impairing the tight coupling of Ca^{2+} channels and synaptic vesicles without changing the properties of Ca^{2+} channels and release machinery *per se*. Such disorganization of active zone was further deteriorated by large reduction in Ca^{2+}-activated large-conductance K^{+}-(BK) channels. Interestingly, activation of GABAB receptors in control synapses prominently blocked Ca^{2+} influx and neurotransmitter release; however, such inhibitory actions were significantly impaired in TKO mice, most likely due to a significant decrease in presynaptic GABAB receptors. Consistently, we found similar phenotypes of deleting all neurexins in hippocampal CA3-CA1 synapses: release probability and GABAB receptor mediated inhibition were impaired when AAV-Cre was selectively injected in hippocampal CA3 to delete all neurexins in pyramidal cells. These results together strongly suggest diverse roles of neurexins in the functional organization of presynaptic active zones.

Disclosures: F. Luo: None. **A. Sclip:** None. **M. Jiang:** None. **T.C. Sudhof:** None.

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186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

Location: Room S401

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 186.05

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH grant 5R01MH094607-05
NIH grant 5R21MH108929-02
NSF Award number 1453799

Title: Synapse formation activates a transcriptional program for the persistent enhancement in the bidirectional transport of mitochondria in the presynaptic neurons

Authors: K. BADAL[1,2], K. AKHMEDOV[1], P. LAMOUREUX[3], X.-A. LIU[1], A. REICH[1], S. SWARNKAR[1], K. MILLER[3], ***S. V. PUTHANVEETTIL**[4];
[1]Scripps Res., Jupiter, FL; [2]Florida Atlantic Univ., Jupiter, FL; [3]Michigan State Univ., East Lansing, FL; [4]The Scripps Res. Inst., Jupiter, FL

Abstract: Mechanisms that regulate the bidirectional transport of mitochondria in neurons for maintaining functional synaptic connections are poorly understood. Here we show that in the pre-synaptic sensory neurons of the *Aplysia*gill withdrawal reflex, the formation of functional synapses leads to persistent enhancement in the flux of bidirectional mitochondrial transport. Importantly, in the absence of a functional synapse, activation of cAMP signaling is sufficient to enhance the bidirectional transport in sensory neurons. Furthermore, the persistent enhancement in transport does not depend on NMDA and AMPA receptor signaling or signaling from the post-synaptic neuronal cell-body, but is dependent on transcription and protein synthesis in the pre-synaptic neuron. We next identified ~4000 differentially enriched transcripts in pre-synaptic neuron suggesting a long-term change in the transcriptional program produced by synapse formation. These results provide novel insights into the regulation of bidirectional mitochondrial transport for synapse maintenance.

Disclosures: K. Badal: None. **K. Akhmedov:** None. **P. Lamoureux:** None. **X. Liu:** None. **A. Reich:** None. **S. Swarnkar:** None. **K. Miller:** None. **S.V. Puthanveettil:** None.

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186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

Location: Room S401

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 186.06

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: WPI-IRCN (JSPS)

Title: Delayed critical period trajectory in the absence of SRGAP2

Authors: *G. A. VARGISH[1], E. SCHMIDT[2], F. POLLEUX[3], T. K. HENSCH[4];
[1]Boston Children's Hosp., Boston, MA; [3]Dept Neurosci., [2]Columbia Univ., New York, NY;
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Abstract: Human brain development is remarkably protracted compared to even our closest evolutionary ancestors. While the evolutionary advantage of structural remodeling lasting well into the third decade of human life remains elusive, such prolonged windows may serve to expand critical period plasticity. Indeed, critical period duration in V1 may scale to the life-span of a given species, yet the mechanisms slowing the trajectory of cortical circuit maturation in humans is largely unknown. Mounting evidence in mice points toward factors controlling the maturation of parvalbumin (PV)-expressing interneurons and their perineuronal nets (PNNs). A prime candidate is slit-robo GTPase activating protein 2 (SRGAP2, or SRGAP2A in humans), one of only 23 genes specifically duplicated in humans. In addition to the ancestral *SRGAP2A* conserved among all mammals, humans also express *SRGAP2C*, a partial duplication that functionally inhibits SRGAP2A. Inactivation of SRGAP2A, by genetic deletion or ectopic SRGAP2C expression in mice, delays synapse maturation and increases dendritic spine and gephyrin cluster density in a dose-dependent fashion *in vitro*, suggesting SRGAP2 may regulate the developmental trajectory of cortical circuits *in vivo*. In SRGAP2 heterozygous (HET) mice, we observed delayed PV circuit maturation and PNN formation in auditory, visual and prefrontal cortices. Consistent with this, whole-cell patch-clamp recordings from layer 4 excitatory principal cells in V1 revealed significant reductions in both spontaneous excitatory and inhibitory postsynaptic currents in juvenile (p25-30), but not adult (>p135), SRGAP2 HET mice. Surprisingly, conditional deletion of SRGAP2 from either excitatory pyramidal (TLCN-Cre) or inhibitory PV (PV-IRES-Cre) cells alone did not phenocopy global mutants, suggesting a non-cell autonomous coordination of circuit maturation. Given that *SRGAP2* mRNA expression is enriched in microglia across species, we examined the density and morphological complexity of microglia in SRGAP2 HET mice and observed an increase in both as compared to WT controls in V1. Taken together, SRGAP2 may regulate the speed of postnatal cortical circuit maturation through a baseline hyper-ramification of microglia that may delay development in SRGAP2 HET mice. This provides a potential evolutionary mechanism for the prolonged neoteny characteristic of human brain development.

Disclosures: G.A. Vargish: None. **E. Schmidt:** None. **F. Polleux:** None. **T.K. Hensch:** None.

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186. Molecular Mechanisms of Synaptogenesis and Activity-Dependent Development

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Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 186.07

Topic: A.06. Synaptogenesis and Activity-Dependent Development

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Pennsylvania Health Research Fund CURE 4100077067
Alfred P. Sloan Fellowship FG-2018-10903
NIH Grant R01-NS110907
Jefferson Synaptic Biology Center

Title: Synaptic maturation requires the gamma-secretase dependent cleavage of a synaptic Wnt receptor

Authors: L. RESTREPO, A. DEPEW, M. PARISI, M. AIMINO, ***T. J. MOSCA**;
Neurosci., Thomas Jefferson Univ., Philadelphia, PA

Abstract: In all nervous systems, newly formed synaptic connections must undergo maturation to transition from structurally simple and functionally unrefined connections to structurally complex entities capable of robust transmission. This is critically important, as maturation failures can underlie neurodevelopmental disorders and intellectual disabilities. At the *Drosophila* neuromuscular junction, a model developing synapse, synaptic maturation is marked by the initial outgrowth of synaptic boutons followed by the acquisition of apposed postsynaptic membrane. Maturation failures are indicated by so-called "ghost boutons" that have presynaptic, but no postsynaptic, architecture. A core pathway that promotes this maturation involves the motoneuron-derived Wnt ligand Wingless binding to the muscle-expressed Frizzled2 (Fz2) receptor. Muscle Fz2 receptors are endocytosed, trafficked to the nuclear periphery, and their C-termini (Fz2-C) are cleaved and imported into the nucleus. This entry promotes postsynaptic development. Though considerable work identified proteins in Fz2 endocytosis, trafficking, and nuclear import, the Fz2-C protease has remained elusive. To identify such genes in maturation, we performed a candidate screen against proteases that when lost, would phenocopy the maturation defects of Fz2 loss. We identified Presenilin and Nicastrin, two subunits of the γ-secretase complex, as essential for synaptic maturation. As γ-secretase is involved in Alzheimer's disease, this suggests maturation and neurodegeneration may be linked. γ-secretase subunits can localize to the postsynapse and their loss results in absent maturation. Synaptic α-spectrin is also markedly decreased, consistent with impaired development. Active zone formation, however, is normal. Further, we identify a behavioral correlate of impaired maturation: altered motility and coordination. Postsynaptic (but not presynaptic) expression of either transgene in their respective mutants rescues these defects, suggesting they function in muscle. In the absence of γ-secretase, Fz2 cleavage is blocked, resulting in impaired nuclear Fz2-C localization; Fz2 expression, endocytosis, and trafficking are otherwise normal. Demonstrating that Fz2-C nuclear entry is key to promoting γ-secretase dependent maturation, muscle expression of pre-cleaved Fz2-C rescues mutant maturation phenotypes. Our data suggests that postsynaptic γ-secretase activity is critical for Fz2 cleavage and maturation. As γ-secretase is associated with Alzheimer's disease, understanding more about its basic function is a significant step towards grasping how it affects human disease.

Disclosures: L. Restrepo: None. **A. DePew:** None. **M. Parisi:** None. **M. Aimino:** None. **T.J. Mosca:** None.

Nanosymposium

187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.01

Topic: A.07. Developmental Disorders

Support: International Rett Syndrome Foundation (IRSF) Grant 3212
Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant 2016-06035
Ontario Rett Syndrome Association (ORSA)

Title: Role of DNA methylation and MeCP2-mTOR signaling in the brain

Authors: *M. RASTEGAR[1], D. KROFT[1], K. SHEIKHOLESLAMI[1,2], M. BUIST[1], A. ALI SHER[1], S. PEJHAN[1], C. OLSON[1];
[1]Dept. of Biochem. and Med. Genet., Univ. of Manitoba, Winnipeg, MB, Canada; [2]Fac. of Med., Univ. of Toronto, Toronto, ON, Canada

Abstract: DNA methylation is an important epigenetic modification with key roles in brain development and function. Accordingly, disruption of normal DNA methylation pattern in the brain is associated with neurodevelopmental disorders and impaired brain function. Three groups of epigenetic factors work in harmony to ensure proper DNA methylation deposition (writers), interpretation (readers), and removal (erasers). In brain, the main DNA methylation “reader” is called “MeCP2”, mutation in which leads to Rett Syndrome (RTT).
RTT is a rare and severe X-linked neurodevelopmental disorder that is mainly found in females. Independent groups (including us) have shown that MeCP2 mutation significantly impacts fundamental cell signaling pathways in the brain, which are important for RTT pathobiology. Recently, our team reported that the MeCP2-mTOR signaling is impaired in the cerebellum of human RTT patients (Olson et al, Frontiers in Genetics 2018)[1]. Here, we hypothesized that molecular abnormalities downstream of MeCP2-mTOR signaling in the brain is region-specific and is associated with abnormal DNA methylation patterns. We performed side-by-side DNA methylation and transcript/protein expression studies for MeCP2-mTOR regulatory network in the cerebellum, amygdala, hippocampus, and cortex of RTT patients and control samples. Our results have led to the identification of potentially novel MeCP2 target genes, few with solid links to the mTOR pathway. Parallel *in vitro* experiments are in progress through MeCP2 gain- and loss-of-function experiments and use of mTOR inhibitors to further establish the MeCP2-mTOR regulation of these target genes. The outcome is expected to be biologically important for future therapeutic application of Rett Syndrome, a severe disease with no cure.
Human RTT and control brain tissues are obtained from NIH NeuroBioBank (neurobiobank.nih.gov). Research with human tissues is reviewed and approved by "University

of Manitoba, Research Ethics Board".
1. Olson CO, Pejhan S, Kroft D, Sheikholeslami K, Fuss D, Buist M, Ali Sher A, Del Bigio MR, Sztainberg Y, Siu VM, Ang LC, Sabourin-Felix M, Moss T, Rastegar M. MECP2 Mutation Interrupts Nucleolin-mTOR-P70S6K Signaling in Rett Syndrome Patients. Front Genet. 2018;9:635.

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Nanosymposium

187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.02

Topic: A.07. Developmental Disorders

Support: UTK Start-up fund
RettSyndrome.org
Office of Research at UTK undergraduate grants

Title: MECP2 regulates hemisphere-specific, subregion-specific expression of perineuronal nets in the adult primary somatosensory cortex in a learned maternal behavior paradigm

Authors: B. Y. B. LAU, D. LAYO, B. EMERY, M. EVERETT, A. KUMAR, P. STEVENSON, K. REYNOLDS, A. CHEROSKY, S.-A. H. BOWYER, S. ROTH, R. P. MCCORD, ***K. KRISHNAN**;
Univ. of Tennessee, Knoxville, TN

Abstract: Rett Syndrome (RTT) is diagnosed as a neurodevelopmental disorder, predominantly affecting 1:10,000 females worldwide. Many of these females live well into their middle ages. RTT is characterized by a short period of typical development, followed by expression of stereotypic sensory, motor, speech and cognitive impairments. RTT is caused by mutations in the X-linked gene methyl CpG-binding protein 2 (MECP2), which regulates chromatin remodeling and gene expression. RTT is hypothesized to be the result of altered synaptic connectivity and plasticity caused by abnormal experience-dependent synapse development and maintenance. These experience-dependent plasticity mechanisms may contribute to sensory processing deficits, which ultimately result in social and cognition impairments. Experimental paradigms to coherently link MECP2 function with hypothesized synaptic plasticity changes to specific behavioral endophenotypes across levels (molecular, cellular, circuit and behavioral) through physiological changes (e.g. early development, puberty, aging) remain underexplored in females. This is a crucial question to answer to determine the pathogenesis of RTT, not only in early postnatal life, but throughout the lifetime of the affected girls and women.

We previously found that lack of MECP2 affects a common neural circuitry motif involving Parvalbumin+ GABAergic neurons and perineuronal nets (PNN), which ultimately results in auditory processing deficits during a pup retrieval task, a feature of learned maternal behavior. Learned maternal behavior is an ethologically-relevant behavior to study complex social communications where mice use multi-modal sensory and motor circuits to navigate their environment. To determine which other brain regions exhibits altered PNN expression before and after surrogacy, we have taken a whole brain immunostaining, imaging and quantification approach. We identified an atypical increase of PNN expression in the primary somatosensory cortex of HETs, before and after learned maternal behavior experience. PNNs are physical substrates for experience-dependent plasticity, which are thought to restrict or facilitate plasticity. We also observe hemispheric- and subregion-specific changes in PNNs, suggesting possible experience-dependent connectivity pattern dysregulation in *Hets*. Taken together, our data suggest that MECP2 deficiency results in atypical expression of PNNs in a context-dependent, hemispheric-specific and region-specific manner, which might result in restrictions in learning new tasks and behaviors.

Disclosures: B.Y.B. Lau: None. **D. Layo:** None. **K. Krishnan:** None.

Nanosymposium

187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.03

Topic: A.07. Developmental Disorders

Support: ProRett Italia
Jerome Lejeune Foundation
Fondazione Umberto Veronesi

Title: Enhancement of activity rescues the early establishment of Mecp2 null neuronal features

Authors: *F. BEDOGNI[1], L. SCARAMUZZA[1], G. DE ROCCO[1,3], C. COBOLLI GIGLI[2], F. CESCA[4], N. LANDSBERGER[5,1];
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Abstract: The X-linked Methyl-CpG-Binding Protein 2 (MeCP2) gene encodes for a multifunctional protein ubiquitously expressed from developmental stages to adulthood. Mutations in *MECP2* are linked to Rett syndrome (RTT), the most common genetic cause of severe intellectual disability in females. Although MECP2 plays a crucial role in the maintenance of proper neuronal functionalities, several evidences now suggest that early signs of the

pathology can be observed (in both humans and animal models) long before the typical RTT symptoms become overt. Focusing on the development of neuronal networks, our data demonstrate that the dynamics of differentiation (both *in vitro* and in pre- and early postnatal cortical tissues) are affected by lack of Mecp2 from a transcriptional, functional and morphological point of view. In fact, we show that the expression of genes encoding for mediators of neuronal activity (such as glutamate receptors and ionic channels) diminishes the magnitude of Ca^{2+} transients induced by exposure to stimuli such as glutamate or NMDA. As a consequence of such defects, and in line with the role played by neuronal activity in driving structural maturity, null neurons display poor morphological complexity, as dendritic arborization and length are reduced. Intriguingly, we demonstrate that strategies aiming at transiently enhancing neuronal activity during critical stages of neuronal network establishment rescues part of the typical defects displayed later by Mecp2 null neurons. Together, our data demonstrate that the impairments affecting adult RTT animal models can be considered the worsening of a condition that is already generated during early development.

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187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.04

Topic: A.07. Developmental Disorders

Support: Rett Syndrome Research Trust HeaRT Grant
Battelle Research Exchange Fellowship
Nationwide Children's Hospital RITA Trainee Research Award Fellowship

Title: A novel *in vitro* modeling system for the study of MeCP2 pathology and treatment response

Authors: *S. L. POWERS[1,2,3], K. KINLEY[1], C. DENNYS-RIVERS[1], R. RODRIGO[1], X. ZHANG[1], S. B. LIKHITE[1], M. J. DUNNING[3], P. R. HEATH[3], L. FERRAIUOLO[3], K. C. MEYER[1,2];
[1]Ctr. for Gene Therapy, Nationwide Children's Hosp., Columbus, OH; [2]Neurosci., The Ohio State Univ., Columbus, OH; [3]Neurosci., Univ. of Sheffield, Sheffield, United Kingdom

Abstract: Rett syndrome (RTT) is an X linked neurodevelopmental disorder affecting approximately 1 in 10,000 girls. Patients exhibit a loss of established developmental milestones and progressive loss of motor function with most adult patients requiring 24/7 supportive care. Cellular pathology is characterized by global compaction of neural somas with shortened and

fewer neurites. Most RTT cases result from loss of function mutations in methyl-CpG binding protein 2 (MeCP2), a ubiquitous transcription factor highly enriched in the central nervous system (CNS) with regulatory functions for thousands of genes. MeCP2 is an important epigenetic reader, binding the majority of 5-methylcytosine residues in the CNS, and recruiting histone deacetylases to remodel chromatin. We previously developed an Adeno-associated virus gene therapy vector expressing human MeCP2 cDNA. We have performed extensive dosing, safety and efficacy studies, demonstrating efficacy in a MeCP2 knockout mouse model and safety in their wild type cohorts and non-human primates. It is clinically apparent that variation in MeCP2 mutations leads to differences in disease severity for RTT patients. However, little research has been done on the impact of remaining misfolded or truncated MeCP2 isoforms on RTT pathology or treatment response. In order to further investigate the role of various MeCP2 mutations on RTT pathology and treatment response, we have developed a novel *in vitro* modeling system utilizing induced neural progenitor cells (iNPCs) directly converted from Rett patient fibroblasts. The direct conversion model is particularly well suited for the study of Rett syndrome because it maintains a greater proportion of epigenetic hallmarks than models developed via induced pluripotency. Using our direct conversion system, we have investigated the non-cell autonomous role of astrocytes in RTT through a co-culture assay with mouse GFP positive neurons using an automated imaging/analysis. Moreover, we performed microarray gene expression analysis and DNA methylation array. We found that RTT astrocytes have a mutation dependent effect on mouse neuron morphology, causing hallmark RTT phenotypes including shortened and fewer neurites. Furthermore, these mutation dependent phenotypes have a basis in differential gene expression profiles. We have also successfully transduced our cells with AAV9 vectors *in vitro* with a robust expression pattern. Our model is well suited for studying the disease mechanisms in RTT, as well as the identification of novel targets for RTT drug discovery and for testing of drugs and gene therapy in a high throughput, patient and mutation specific manner.

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187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.05

Topic: A.07. Developmental Disorders

Title: Identifying potential therapeutics against Rett syndrome using a highly homogeneous 3-dimensional high-throughput screening platform

Authors: P. NEGRAES[1], N. SODHI[1], S. ROMERO[1], F. ZANELLA[2], ***C. CARROMEU**[2]; [1]StemoniX, San Diego, CA; [2]Stemonix, San Diego, CA

Abstract: Rett Syndrome (RTT) is a progressive neurodevelopmental disorder caused by mutations in the X-linked gene MeCP2. Recent scientific discoveries have greatly advanced our understanding of the disease's mechanism. However, efforts to translate this understanding into effective therapeutics have been mostly unsuccessful. One hurdle is the lack of a human *in vitro* high-throughput screening (HTS) system that can efficiently screen large compound libraries in a reproducible fashion. Such a platform must be able to capture the complexities of human neurodevelopment and recapitulate RTT phenotypes *in vitro*. We recently developed a highly homogenous 3D neural HTS system employing a functional phenotype readout (microBrain 3D). The platform relies on neurospheroids derived from human induced pluripotent stem cells (hiPSCs) and comprise a balanced culture of cortical neurons and astrocytes. Each spheroid presents spontaneous, synchronized, detectable, and quantifiable calcium oscillations. Moreover, we developed a kinetic high-throughput assay compatible with commercially available cellular screening platforms, such as the FLIPR Tetra® system, that is able to simultaneously detect these calcium oscillations across the whole 384-well plate. The platform has been optimized to be highly homogenous and consistent across wells, plates, and batches. Here, we describe the use of this platform to investigate the neurodevelopmental disorder RTT. When introducing hiPSCs derived from RTT patients into our platform, a clear functional disease phenotype was observed. RTT 3D neural cultures displayed calcium signal that indicates a compromised neural network. Using a targeted library of 296 compounds (SMART library), we were able to identify some targets that alleviated the altered phenotype observed in RTT spheroids. In summary, our work has the potential to dramatically change today's translational research field for neurodevelopmental disorders and to point to new effective therapies for RTT.

Disclosures: **P. Negraes:** A. Employment/Salary (full or part-time):; StemoniX. **N. Sodhi:** A. Employment/Salary (full or part-time):; stemonix. **S. Romero:** A. Employment/Salary (full or part-time):; Stemonix. **F. Zanella:** A. Employment/Salary (full or part-time):; Stemonix. **C. Carromeu:** A. Employment/Salary (full or part-time):; StemoniX.

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187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.06

Topic: A.07. Developmental Disorders

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Rett Syndrome Research Trust Seed Funding (JDM)
NIH Grant Pioneer DP1 NS106665 (JDM)
Emily and Robert Pearlstein Fund (JDM)
Max and Anne Wien Professorship (JDM)

Title: Vitamin D supplementation rescues aberrant NF-kB pathway activation and partially ameliorates Rett syndrome cortical phenotypes in Mecp2 mutant mice

Authors: *M. C. RIBEIRO[1], S. M. MOORE[1], J. D. MACKLIS[2], J. L. MACDONALD[1]; [1]Dept. of Biology, Program in Neurosci., Syracuse Univ., Syracuse, NY; [2]Dept of Stem Cell and Regenerative Biology, and Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: Rett syndrome (RTT) is a severe, progressive X-linked neurodevelopmental disorder caused by mutations in the transcriptional regulator MECP2. *Mecp2* loss-of-function leads to increased activation of the NF-kB pathway in the CNS, which contributes to the aberrant morphology observed in cortical layer II/III projection neurons of the neocortex. Genetically attenuating NF-kB signaling in the *Mecp2*-null cortex rescues some of the characteristic neuronal phenotypes of *Mecp2*-null cortical projection neurons, including reduced dendritic complexity and soma area. These results raise the intriguing question of whether NF-kB pathway inhibitors can also partially rescue RTT phenotypes. Among the many known inhibitors of the NF-kB pathway is vitamin D, and, strikingly, vitamin D deficiency is prevalent in RTT patients. Our data show that *Mecp2*-null mice similarly have significantly reduced total serum levels of 25(OH)D compared to wildtype littermates. Further, treating cortical neurons *in vitro* with calcitriol, the activated form of vitamin D, increases the reduced neurite outgrowth observed after *Mecp2* knockdown, and decreases p65 nuclear translocation, which is indicative of NF-kB pathway activation. Thus, to investigate whether vitamin D supplementation reduces the aberrant NF-kB activity in *Mecp2*-null cortex *in vivo*, and might have therapeutic benefit, we treated both male *Mecp2* hemizygous null, female *Mecp2* heterozygous mice and wildtype littermates with control or vitamin D supplemented chow, beginning at an early symptomatic stage of 4 weeks. This dietary supplementation significantly increases total serum levels of 25(OH)D in both *Mecp2*-null and wildtype mice. Strikingly, 8-week-old *Mecp2*-null mice on vitamin D supplemented chow show rescued dendritic complexity, soma area and dendritic spine density of cortical projection neurons when compared to *Mecp2*-null mice on control chow. Similar neuronal morphological rescue is observed with vitamin D supplemented chow in 5-month-old heterozygous female mice, which better recapitulate the condition in humans; behavioral analyses and investigation of optimal therapeutic time windows are currently underway. Thus, our data suggest that vitamin D could be a simple, and cost-effective, partial therapeutic avenue for RTT by reducing NF-kB signaling.

Disclosures: M.C. Ribeiro: None. **S.M. Moore:** None. **J.D. Macklis:** None. **J.L. MacDonald:** None.

Nanosymposium

187. Rett Syndrome: New Mechanisms and Potential Therapeutics

Location: Room S403

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 187.07

Topic: A.07. Developmental Disorders

Support: NIH ES 100221
Rettsyndrome.org

Title: MECP2 deletion prematurely restricts a novel window of hippocampal synaptic plasticity

Authors: K. E. CARSTENS[1], D. J. LUSTBERG[2], E. K. SHAUGHNESSY[1], K. E. MCCANN[1], G. M. ALEXANDER[1], *S. M. DUDEK[1];
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Abstract: Developing neural circuits are shaped by experience in early postnatal life and are particularly sensitive to disruption during certain critical periods of plasticity. The exact mechanisms underlying these sensitive periods are not fully understood, but one candidate is a specialized form of extracellular matrix, referred to as perineuronal nets (PNNs). PNNs have been implicated in inhibiting structural and functional plasticity and have been linked to several disorders with severe learning impairments, including the neurodevelopmental disorder Rett Syndrome. PNNs are usually localized around inhibitory neurons in the hippocampus and elsewhere, but in addition, PNNs densely surround a population of excitatory neurons in mouse hippocampal area CA2. CA2 stratum radiatum synapses are unusually resistant to induction of long-term potentiation (LTP), and recently we had identified PNNs as a negative regulator of LTP there. PNNs in CA2 appear postnatally in mice, prompting us to examine plasticity prior to postnatal day (PN)14 when PNNs are usually first detected. We found that LTP could be induced at CA2 synapses at these younger ages (PN 8-11), suggestive of a novel window of plasticity in the hippocampus. Next, we investigated how PNNs may be altered during development in mice lacking MECP2. We found that PNN staining in CA2 was more intense in the MECP2 KO mouse compared to control littermates, starting from PN14. In addition, PNNs in CA2 developed abnormally early in MECP2 KO mice, coincident with a premature down-regulation of LTP in CA2. Given that this effect may be activity-regulated, we then investigated if directly increasing or decreasing activity of CA2 neurons in adult mice *in vivo* using chemogenetics alters PNNs. We found that increasing CA2 activity for 5 days decreased PNN staining intensity, whereas decreasing activity for 5 days increased PNN staining intensity in CA2. These results suggest that pathological increases in neuronal activity, like that observed in Rett Syndrome, are not likely to be responsible for the increased deposition of PNNs in CA2. Moreover, analysis of hippocampal mRNA at PN10 and PN18 revealed significant differences in gene expression in MECP2 KO versus WT. Interestingly, social discrimination was not significantly different between MECP2 KO and control mice at PN35, suggesting that abnormal development of PNNs

and plasticity in CA2 do not impact this measure of behavior at this age. Overall, the presence of PNNs in CA2 is highly suggestive of a critical period of plasticity in the hippocampus that may ultimately reveal insights into hippocampal-dependent learning impairments that emerge in Rett syndrome infants.

Disclosures: K.E. Carstens: None. **D.J. Lustberg:** None. **E.K. Shaughnessy:** None. **K.E. McCann:** None. **G.M. Alexander:** None. **S.M. Dudek:** None.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.01

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: VA Merit Award to Douglas L. Feinstein

Title: Making sense of genetic risk factors in multiple sclerosis

Authors: *A. I. B. BOULLERNE, D. L. FEINSTEIN;
Anesthesiol., Univ. of Illinois at Chicago, Chicago, IL

Abstract: Aiming to determine the genetic burden of a family heavily affected by multiple sclerosis (MS), we undertook a search for reliable risk factors. Over the past decade, the International Multiple Sclerosis Genetics Consortium (IMSGC) has considerably invested to crack MS genetic susceptibility, enrolling thousands of patients and healthy subjects, coordinating the collaborative international effort of hundreds of clinicians, as well as providing enormous financial resources. A number of high profile publications resulted in a provisional list of 110 autosomal non-hla risk factors. These genetic variants were warrantied by the largest patient-control populations of European ancestry possibly attainable throughout the world to reach statistical significance by genome-wide association study (gwas). However, an ultimate addition of few thousands subjects (from 29k to 47k cases and 51k to 68k controls) drastically changed the latest list for MS susceptibility to 200 new autosomal non-hla variants. Strikingly, we discovered that only 8 single nucleotide polymorphisms (snp) were shared between the newest and former list of 110 snps published by IMSGC in 2013. Assuming such a discrepancy would be resolved at the locus level, we launched a careful investigation of all 302 IMSGC snps, using the most up-to-date NCBI graphical viewer based on the latest human reference genome version. Using a liberal 10 kb window for each snp within a protein-coding gene (from 5 kb upstream to 5 kb downstream), we surprisingly found that only 50 loci were shared between the 2013 and 2017 IMSGC lists. Some 23 intergenic loci and 31 genes were abandoned by the new 200 snps. Among them, GALC gene (Fig.) was not retained, despite being formerly selected several times, and most recently again by an IMSGC exomic array for rare variants. In parallel,

variants significant for MS susceptibility and/or severity are routinely published by independent investigators, using smaller patient-control cohorts of narrower ancestry in the diverse European mosaic, and hypothesis-driven snp selection as opposed to gwas exploration. None of these 'independent' snps is among the mighty IMSGC 302 set. Complicating further, gwas-derived minor alleles giving MS susceptibility do not always correspond to world minor alleles reported in 100 Genomes and HapMap projects. It is currently not realistic to determine the genetic burden of an individual with MS. This work was supported by a VA Merit Award to Douglas L. Feinstein.

Disclosures: A.I.B. Boullerne: None. **D.L. Feinstein:** None.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.02

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Histone modifications induce a neuroinflammatory response in X-linked dystonia Parkinsonism

Authors: *T. PETROZZIELLO[1], A. N. MILLS[1], C. A. VAINE[2], E. B. PENNEY[2], C. D. BRAGG[2], G. SADRI-VAKILI[1];
[1]NeuroEpigenetics Laboratory, Healey Ctr. for ALS at Mass General, Massachusetts Gen. Hosp., Boston, MA; [2]Dept. of Neurology, Massachusetts Gen. Hosp., Boston, MA

Abstract: Neuroinflammation plays a key role in several neurodegenerative diseases and recent findings suggest that it may also be involved in X-linked Dystonia Parkinsonism (XDP). Indeed, both fibroblasts and neuronal stem cells (NSCs) derived from XDP patients demonstrated hypersensitivity to TNFα and a dysregulation in NFkB signaling pathway. However, the mechanisms underlying these inflammatory alterations remain unclear. We have begun to probe neuroinflammatory mechanisms with a focus on epigenetic modifications given that intronic retroelements that play a key role in XDP pathogenesis are able to interfere with transcription by altering the local chromatin landscape.
Specifically, our results demonstrate a significant increase in histone H3 acetylation, cleavage, and deamination (or citrullination) in human post-mortem XDP prefrontal cortex compared to controls. These specific histone modifications are linked to increases in neutrophil extracellular trap (NET) formation or NETosis, a process widely associated with inflammation. Accordingly, our results demonstrated an increase in both peptidylarginine deaminase 2 (PAD2) and 4 (PAD4), enzymes that catalyze histone citrullination, in human post-mortem XDP prefrontal cortex compared to controls.
Similarly, there was a trend towards an increase in cathepsin D, a lysosomal protease involved in

histone cleavage. Lastly, PAD2 and cathepsin D levels showed a trend towards an increase in fibroblasts derived from XDP patients compared to controls. Taken together, our results suggest an increase in the neuroinflammatory response in XDP brain and have identified new potential targets for developing therapies as well as biomarkers of disease.

Disclosures: T. Petrozziello: None. **A.N. Mills:** None. **C.A. Vaine:** None. **E.B. Penney:** None. **C.D. Bragg:** None. **G. Sadri-Vakili:** None.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.03

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant NS104560

Title: Novel phenotype-specific plasma biomarkers in x-linked adrenoleukodystrophy

Authors: *J. SINGH[1], A. FATEMI[2], L. M. POISSON[3], S. GIRI[4], N. TIWARI[1];
[1]Neurol., HENRY FORD HEALTH SYSTEM, Detroit, MI; [2]Neurol., Johns Hopkins Univ., Baltimore, MD; [4]Neurol., [3]Henry Ford Hlth. Syst., Detroit, MI

Abstract: Introduction: X-linked adrenoleukodystrophy (X-ALD) is the most frequent inherited monogenic demyelinating disease (minimal incidence 1:17,000). X-ALD is defined by two major phenotypes in males; 1) the fatal cerebral adrenoleukodystrophy (ALD), and 2) the relatively benign adrenomyeloneuropathy (AMN). In February 2016, X-ALD was added to the Recommended Uniform Screening Panel, a federal list of all genetic diseases recommended for state newborn screening programs. Yet, there are no biomarkers to predict the onset of AMN and ALD. The objective of this study is to identify a unique panel of plasma biomarkers predictive of the AMN and ALD phenotypes in male patients diagnosed with X-ALD.
Methods: Healthy controls (CTL), AMN and ALD patient'splasma samples (n=10) obtained from the Moser Center for Leukodystrophies, Kennedy Krieger Institute, Baltimore, were processed for metabolite extraction and analysis (Gas Chromatography Mass Spectrometry (GC-MS)). The same specimens were assayed for micro-RNA (miRNA) abundance (miRNA sequencing).Data analyses wereperformed in R (v 3.5, https://www.r-project.org/) with pathway analysis by "MetaboAnalyst"(v 4.0, www.metaboanalyst.ca/). Each measured metabolite was screened using appropriate analysis of variance (ANOVA) models to account for the study design. Thresholds for significance were set to control the estimated false discovery rate, per platform, at 5%.
Results: Of the 860 metabolites measured, 190 metabolites altered across all the 30 cases (ANOVA F-test, FDR<0.05). Comparing CTL with AMN by post-hoc t-test, 27 metabolites

were significantly altered, whereas 35 metabolites were significantly altered between AMN and ALD patient plasma.Among 2545 miRNA measured, 95miRNA were significantly altered. Of these, 35 were altered between CTL and AMN and 30 were altered between AMN and ALD. Further analysis by incorporating disease status data (expanded disability status scale and Loes severity score for extent of demyelination) is ongoing and will included at the time of presentation.
Conclusion: This is the first report of plasma biomarkers of disease phenotypes in X-ALD and raises the possibility of phenotype prediction in newborns diagnosed with X-ALD.

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Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.04

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: A Cure for Ellie

Title: Gene expression analysis reveals significant neuroinflammatory mechanisms in the LBSL mouse

Authors: *C. L. NEMETH[1], S. N. TOMLINSON[1], M. JAIN[2], B. M. O'BRIEN[1], A. S. FINE[3], L. LEBON[4], K. MARTIN[4], C. SIDRAUSKI[4], A. TRIFUNOVIC[5], A. FATEMI[1];
[1]Moser Ctr. for Leukodystrophies, [2]Dept. of Bone and Osteogenesis Imperfecta, [3]Dept. of Neurol. and Developmental Med., Kennedy Krieger Inst., Baltimore, MD; [4]Calico Labs LLC, South San Francisco, CA; [5]Inst. for Mitochondrial Dis. and Aging, CECAD Res. Ctr., University of Cologne, Germany

Abstract: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare, autosomal recessive disorder characterized by slowly progressive spasticity, ataxia, proprioceptive deficits, and in some cases, cognitive decline. Most patients harbor compound heterozygous mutations in the *DARS2* gene which encodes mitochondrial aspartyl-tRNA synthetase, a ubiquitously expressed enzyme which charges tRNA molecules with cognate amino acids essential for mitochondrial protein translation. It remains unclear why certain tissues and cell types appear more vulnerable to *DARS2* deficiency or how this translates into typified patterns of demyelination in patients. Conditional deletion of *Dars2* in CamKIIα-expressing neurons of the cortex and hippocampus of mice results in a hyperactive behavioral phenotype, progressive and severe cortical atrophy, neuronal loss, and significant cortical and hippocampal microglial activation. By nine months of age, mice exhibit an increased number of

IBA1+ cells with a decreased overall cellular area suggesting an amoeboid, activated state ($p < 0.05$). Gene expression analysis of cortical tissue prior to the onset of symptoms confirms profound inflammatory and immune activation. Even at this early time point (14 weeks), significantly altered transcripts are in agreement with microglial activation and cytokine release, however most notable is the over 200-fold increase in cystatin F (*Cst7*; log2 fold change of 7.284) and its main target, cathepsin C (*Ctsc;* 1.84 log2FC). Cystatin F, a papain-like lysosomal cysteine protease inhibitor involved in immune regulation during disease, is not normally expressed in the healthy brain, but has been detected in areas of active de- or remyelination in various rodent models as well as in human multiple sclerosis tissue. Cathepsin C is similarly upregulated during inflammatory states and is a known regulator of T-lymphocytes, cells similarly implicated in chronic neurodegenerative processes such as demyelination and axonal loss. Although the involvement or expression of cystatin F and cathepsin C in LBSL patients is unknown, selective depletion of *Dars2* in mouse excitatory cortical neurons produces a sequalae consistent with observed patterns of white matter injury. These identified targets may be avenues of investigation for the better understanding of LBSL disease progression, and importantly, disease intervention.

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Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.05

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant 2R15NS060117-02

Title: Brassicaceae and Asteraceae plants (kale, arugula, dandelion) moderates changes in sulfate-reducing bacteria, Desulfovibrionaceae, in the gut microbiome and reduces inflammation in diet-induced obese pre-diabetic C57BL/6 mice

Authors: *B. TENG, D. FOSTER, A. OYETUNDE, P. SONI, T. SIMON, P. GHOTRA, L. R. BANNER;
California State Univ. Northridge, Northridge, CA

Abstract: World obesity rates have fundamentally shifted in the last few decades. An increase in high-fat consumption along with a decrease in physical activity is the primary driver leading the obesity epidemic. Diet-induced obesity predisposes individuals to type-2 diabetes and

contributes to complications including those of the nervous system and the immune system. Diabetes is associated with an elevated risk for neurodegeneration and dementia and changes in hippocampal plasticity. Studies have shown that neurodegeneration caused by diabetes is related in part, to elevated levels of inflammatory cytokines involved in brains of animals fed a high-fat diet (HFD). Also, it is well documented that a high-fat diet causes changes in gut microbiota. The dysbiosis of gut microbiota triggers a pro-inflammatory response and may also disrupt neuronal signaling. While diabetes caused by diet-induced obesity is mostly preventable by reducing high fat intake, individuals often find it difficult to change unhealthy aspects of their diet radically. Instead, we are proposing to alter the imbalance of gut microbiota through supplementation of kale, arugula (f. Brassicaceae) and dandelion (f. Asteraceae) plants to mediate the inflammatory response, potentially taper neurodegeneration, and thus stymie cognitive decline. To address this issue, C57BL/6 mice were fed either a control or high-fat diet (HFD)(60% fat) for 18 weeks until the HFD group reached a pre-diabetic stage. After 18 weeks, mice on a HFD became obese, showed signs of metabolic syndrome, and showed deficits in spatial learning. For the next 20 weeks, the diets of all the mice were supplemented daily with kale, arugula, or dandelion, during which, the mice were subjected to multiple repetitions of the Morris Water Maze, and Nonconditioned Social Discrimination Procedure, to probe for changes in their memory. Fecal samples before and after supplementation of Brassicaceae and Asteraceae plants were collected, and changes in gut microflora were characterized by 16S rRNA gene sequencing for bacterial identification. Our data shows that mice fed a HFD and supplemental greens maintained their phylogenetic bacterial alpha diversity, while mice solely fed a HFD saw a decrease. Notably, levels of sulfate-reducing bacteria, Desulfovibrionaceae, increased in the group fed strictly a HFD, while groups fed supplemental greens mimicked levels of their pre-HFD state. This implies, by modulating Desulfovibrionaceae levels, a potential mechanism to reduce endotoxins from the gut microbiome and may show the supplemental greens may protect or slow the progression of the dysbiosis of the gut microbiome that is typical of a HFD.

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Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.06

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: HL52141
Stanford Discovery Innovation Award

Title: Glial mitochondria released after dysregulated fission propagate inflammatory neurodegeneration

Authors: A. U. JOSHI[1], P. S. MINHAS[1], S. LIDDELOW[2], B. HAILESELASSIE[1], K. I. ANDREASSON[1], *D. MOCHLY-ROSEN[1];
[1]Stanford Univ., Stanford, CA; [2]NYU Langone Med. Ctr., New York, NY

Abstract: In neurodegenerative diseases, debris of dead neurons are thought to trigger glia-mediated neuroinflammation, thus increasing neuronal death. Here, we show that expression of neurotoxic proteins associated with these diseases in microglia alone is sufficient to trigger death of naïve neurons directly and to propagate neuronal death through activation of naïve astrocytes to A1 state. Injury propagation is mediated, in great part, by the release of fragmented and dysfunctional microglial mitochondria to the neuronal milieu. The amount of damaged mitochondria released from microglia relative to functional mitochondria and the consequent neuronal injury are determined by Fis1-mediated mitochondrial fragmentation within the glia cells. The propagation of inflammatory response and neuronal cell death by extracellular dysfunctional mitochondria suggests a potential new intervention for neurodegeneration - one that inhibits mitochondrial fragmentation in microglia, thus inhibiting the release of dysfunctional mitochondria into the extracellular milieu of the brain, without affecting the release of healthy neuroprotective mitochondria.

Disclosures: **A.U. Joshi:** None. **P.S. Minhas:** None. **S. Liddelow:** None. **B. Haileselassie:** None. **K.I. Andreasson:** None. **D. Mochly-Rosen:** None.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.07

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

Support: A grant-in-aid for the Cooperative Research Project from the Institute of Natural Medicine at the University of Toyama in 2014 and 2015
Discretionary Funds of the President of the University of Toyama
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2018 Director Leadership Expenses from the Institute of Natural Medicine at the University of Toyama
National Natural Science Foundation of China, Grant/ Award Number: 81803753

Title: Naringenin promotes aβ clearance and ameliorates cognitive deficiency in Alzheimer’s disease and underlying mechanisms

Authors: *Z. YANG[1,2], T. KUBOYAMA[2], C. TOHDA[2];
[1]Inst. of Marine Drugs, Guangdong Ocean Univ., Zhanjiang, China; [2]Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan

Abstract: Activated microglia are categorized as classical M1 and alternative M2 phenotypes. M2 microglia play important roles in Aβ clearance and memory recovery in Alzheimer's disease (AD). Therefore, increasing of M2 microglia is expected to recover from AD. Our recently study showed that Drynaria Rhizome (DR) water extract and its derived blood-brain barrier penetrating metabolite naringenin, decreased Aβ deposits and recovers memory function in transgenic AD mice model, 5XFAD. In this study, we aim to investigate potential effects of naringenin on microglial polarization and to reveal the underlying mechanisms of Aβ reduction.
Primary cultured cortical microglia were treated with Aβ1-42 (1 μM) for 24 hours, following administration of naringenin (0.1-100 μM) for another 24 hours, then the microglia were fixed and immunostained with CD206 (M2 marker) and iNOS (M1 marker). Naringenin remarkably promoted M2 microglia polarization ($CD206^+$ $iNOS^-$) and inhibited Aβ1-42-induced M1 microglia ($CD206^-$ $iNOS^+$) activation.
Since microglia reportedly played a critical role in cerebral Aβ clearance through Aβ degradation enzymes after phagocytosis, we investigated the expression of Aβ degradation enzymes. Primary cultured cortical microglia were treated with naringenin (50 and 100 μM) for 24 hours, then the microglia were fixed and immunostained with insulin degradation enzyme (IDE) or neprilysin (NEP), and Arginase I (M2 marker), CD16/32 (M1 marker). As the result, after naringenin treatment, NEP and IDE were downregulated in M1 microglia and upregulated in M2 microglia. Our results indicated that naringenin increased Aβ degradation enzymes in M2 microglia, probably leading to Aβ plaque reduction.
Peroxisome proliferator-activated receptor γ (PPARγ) is involved in the regulation of macrophage differentiation and activation in the peripheral organs and microglial activation and function in central nervous system. In order to clarify how naringenin regulates M2 microglia polarization and Aβ degradation enzymes expression, we investigate the effect of naringenin on peroxisome proliferator-activated receptor γ (PPARγ). BV2 microglia were treated with Aβ1-42 (5 μM) for 24 hours, following administration of naringenin (10-100 μM) for another 24 hours. Naringenin remarkably inhibited Aβ1-42-induced PPARγ reduction. The direct target of naringenin in microglia and exactly mechanism of naringenin are under investigation.

Disclosures: Z. Yang: None. **T. Kuboyama:** None. **C. Tohda:** None.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.08

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant 1-UG3-TR-002198-01

Title: Human Brain-Chip: Modeling functions of the human blood-brain barrier and inflammation

Authors: K. KODELLA, D. V. MANATAKIS, C. HINOJOSA, G. A. HAMILTON, K. KARALIS, ***I. PEDIADITAKIS**;
Emulate Inc., Boston, MA

Abstract: Species differences in brain function and blood-brain barrier (BBB) often precludes accurate extrapolation from animal models to the clinic. We have an unmet need for human relevant systems that can better emulate key aspects of human brain physiology and pathophysiology and that could be applied to model critical aspects of disease mechanisms, associated with neuroinflammation. We have developed a Brain-Chip, a microengineered system designed to more faithfully recapitulate key structural and functions of human *in-vivo* neural tissues than conventional cell-based models or animal models. The Brain-Chip incorporates key features of the brain vascular microenvironment, including mechanical forces induced by shear stress, tissue-specific extracellular matrix, and the cytoarchitecture of normal brain microvasculature. We provide evidence that this complex Brain-Chip model can support co-culture of human iPSC-derived neurons and primary glia cells (astrocytes and microglia) that are able to establish extensive networks in the neuronal channel. Brain endothelial cells successfully maintained at the vascular channel of the Brain-Chip in the presence of fluidic shear stress (to provide *in vivo* relevant mechanical forces) exhibited hallmark features of the human BBB, such as development of complex tight junctions and minimal barrier permeability. Exposure to an inflammatory trigger, tumor necrosis factor-alpha (TNF-α), increased paracellular permeability, glia activation and the corresponding secretion of proinflammatory cytokines. In summary, our findings so far suggest that the Brain-Chip is a suitable model for the study of neuroinflammation and other disorders associated with altered BBB permeability.

Disclosures: **K. Kodella:** A. Employment/Salary (full or part-time):; Emulate Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc.. **D.V. Manatakis:** None. **C. Hinojosa:** A. Employment/Salary (full or part-time):; Emulate Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate nc. **G.A. Hamilton:** A. Employment/Salary (full or part-time):; Emulate Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **K. Karalis:** A. Employment/Salary (full or part-time):; Emulate Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc. **I. Pediaditakis:** A. Employment/Salary (full or part-time):; Emulate Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Inc..

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.09

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Adelson Medical Research Foundation (to LB)
MTEC (to LB: J.L. Goldberg, PI)
Natural Science Foundation of China (NSFC 81770930 to Bing Jiang)
China Hunan Provincial Science and Technology Department (No. 2018SK2131)

Title: Effects of CNTF gene therapy on optic nerve regeneration and RGC survival involve neuroinflammation and other growth factors

Authors: *L. XIE, Y. YIN, H.-Y. GILBERT, L. I. BENOWITZ;
Harvard Med. Sch., Boston, MA

Abstract: Ciliary neurotrophic factor (CNTF) is a therapeutic candidate for several neurodegenerative diseases, and its neuroprotective effects and mechanisms of action have been widely explored. Intraocular injection of recombinant CNTF (rCNTF) is generally found to induce only low levels of optic nerve regeneration unless SOCS3 (suppressor of cytokine signaling 3) is deleted in retinal ganglion cells (RGCs). On the other hand, AAV-mediated CNTF expression in RGCs induces strong regeneration. Intravitreal virus injections induce moderate intraocular inflammation, and CNTF is a known chemoattractant. We therefore tested the possibility that the beneficial effects of AAV- mediated CNTF delivery are to some extent due to intraocular inflammation and its associated pro-regenerative and neuroprotective factors. Consistent with other reports, we showed that intravitreal rCNTF induced little axon regeneration, whereas AAV2-CNTF had strong effects. Compared with controls, AAV2-CNTF attracted inflammatory cells, particularly in the optic nerve head, and increased mRNA levels for inflammation-related growth factors, stromal derived factor 1 (SDF1) (2.5X) and oncomodulin (Ocm) (2.2X), and CD68 (3.2X) in whole eye. SDF1 was expressed in both IB4/vWF+ vascular cells and F4/80+ macrophages, whereas Ocm was detected in Gr1+ neutrophils. Blocking SDF1 and Ocm diminished AAV2-CNTF-induced axon regeneration and RGC survival. Therefore, Inflammation plays a significant role in the pro-regenerative and neuroprotective effects of AAV-mediated CNTF delivery after optic nerve injury.

Disclosures: L. Xie: None. **Y. Yin:** None. **H. Gilbert:** None. **L.I. Benowitz:** None.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.10

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

Title: Modeling human Alzheimer's diseases (AD) with human iPSC neurons, astrocytes, and microglia

Authors: *B. CHIH, R. A. BASSIL, K. SHIELDS, S. NG PALACE;
Biochem. and Cell. Pharmacol., Genentech Inc, South San Francisco, CA

Abstract: The two key human brain pathological hallmarks of Alzheimer's disease (AD) are amyloid beta (Aβ) plaques and tau fibrillary tangles. Unfortunately, transgenic mouse models of AD have failed to faithfully recapitulate these two pathologies together, making it challenging for drug development. A humanized AD cellular model could potentially capture both pathologies. We generated a robust, consistent, and long term (3-months+) human iPSC neuronal culture platform in 384 wells plates for unbiased high content image analysis. We implemented robotic automation to systematically and reproducibly maintain human neurons. High content imaging was conducted to analyze cellular phenotypes. Thousands of neurons were imaged per well and 4 wells per condition. Our *in vitro* human iPSC AD model manifested several disease-related phenotypes, including synapse loss, dendrite retraction, axon fragmentation, phospho-tau translocation to the somatodendritic compartment, and finally neuronal cell death. Anti-Aβ antibody protected neurons from all these pathologies even late-stage AD pathology phenotypes such as tau phosphorylation and neuronal death. This result supported the intimate link between Aβ toxicity and Tau pathology. To further validate this AD model, small molecules inhibitors to known kinases in the AD signaling pathways were tested and also conferred protection. This indicates that AD pathological signaling events are preserved in this system. Surprisingly, we also found the formation of Aβ plaque-like structures that are Aβ plaque dye positive in the absence of microglia. Furthermore, neurofilament and phosphor-tau staining revealed swollen and dystrophic neurites surrounded a subset of these Aβ plaques resembling human AD neuritic plaques. Incorporating human primary or iPSC microglia, we found that microglia surrounded the Aβ plaques and reduced the number and size of the plaques. Furthermore, human microglia also blocked the dystrophic neurite formation. Human microglia co-culture conferred ~30% protection from synapse loss and p-tau induction in this AD model. Interestingly, we also found that microglia can synergize with antibody to protect human neurons through antibody effector function. This human iPSC AD model has recapitulated key AD pathologies and key cellular phenotypes between neurons, astrocytes and microglia. This model will facilitate target discovery and drug development efforts.

Disclosures: **B. Chih:** A. Employment/Salary (full or part-time):; Genentech. **R.A. Bassil:** A. Employment/Salary (full or part-time):; Genentech. **K. Shields:** A. Employment/Salary (full or part-time):; Genentech. **S. Ng Palace:** A. Employment/Salary (full or part-time):; Genentech.

Nanosymposium

188. Neuroinflammation: Mechanisms and Therapeutic Strategies

Location: Room N427

Time: Sunday, October 20, 2019, 1:00 PM - 3:45 PM

Presentation Number: 188.11

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: A phase 1b multiple ascending dose study of elezanumab in multiple sclerosis patients reveals biomarker profiles consistent with CNS target engagement and a neurorestorative mechanism of action

Authors: *T. P. MISKO[1], Y. FANG[2], M. SALTARELLI[3], M. SCHULZ[4], J. SCHMIDT[5], J. SAVARYN[5], K. AWWAD[4], J. MOLLON[4], M. DROESCHER[4], J. BERNHARD[4], H. V. KALLURI[5], M. ROSEBRAUGH[5], X. QI[5], C. LOCKE[5], I. DREHER[4], A. ZIEMANN[6]; [1]Translational Neurosci., Abbvie Neurosci. Develop., North Chicago, IL; [2]Abbvie Inc, Redwood City, CA; [3]Abbvie Inc, Worcester, MA; [4]Abbvie Inc, Ludwigshafen, Germany; [6]Neurosci. Develop., [5]Abbvie Inc, North Chicago, IL

Abstract: Although disease-modifying therapies (DMT) in MS have served a great unmet medical need, patients may require neurorestorative therapies (NRT) to reduce their level of disability. Repulsive guidance molecule A (RGMa) has been shown to be upregulated in numerous neurological disorders, including multiple sclerosis (MS). This upregulation appears to be linked to inhibition of axonal growth and oligodendroglial maturation contributing to demyelination and to increased functional disability arising from neurologic damage. Elezanumab, a fully human monoclonal antibody directed against RGMa, was studied in subjects (n = 20) with MS (placebo, 150 mg, 600 mg, 1800 mg monthly) in a Phase 1b multiple ascending dose study (M14-173) to characterize its PK, tolerability and safety profile. In addition, the M14-173 study was used to identify biomarkers supporting CNS target binding/engagement as well as those consistent with a neurorestorative mechanism of action. CSF soluble free RGMa (unbound by elezanumab) decreased and CSF total RGMa increased with increasing concentrations of elezanumab, indicating CNS target binding. Consistent with anti-RGMa-mediated Rho kinase pathway inhibition and a subsequent neuroregenerative response, increased CSF levels of interleukin-10 (IL-10) correlated with increasing elezanumab CSF exposure. In contrast, CSF levels of neurofilament light (NFL), a well-characterized marker of neurodegeneration, decreased at CSF exposures of elezanumab ranging from 1000 to 3000 ng/ml. Furthermore, elevated CSF levels of ubiquitin carboxy-terminal hydrolase L1 (UCHL1), an enzyme linked to neuronal survival and synaptic integrity, correlated well with elezanumab exposure. Metabolomic analysis of CSF revealed an apparent elezanumab-associated reduction in glutamate levels, a result also supporting a neuroprotective response to therapy. In summary, the biomarker response to elezanumab treatment in the M14-173 study suggests both CNS target binding and target engagement through upregulation of pathways downstream from RGMa blockade that are consistent with remyelination, neuroregeneration and neuroprotection. Notably, these apparent exposure-dependent effects occurred during a relatively brief course of therapy (four months). Importantly, these findings inform dose selection for ongoing Phase 2 proof of

concept studies and identify biomarker profiles that may support the interpretation of mechanism-based Phase 2 clinical outcomes.

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Nanosymposium

189. Neurodegeneration and Injury II

Location: Room S103

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 189.01

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

Support: Doctoral Programme in Molecular Medicine at the University of Eastern Finland

Title: High-fat diet leads to memory impairment and decreased insulin-Akt-GSK3β signaling in the brain of transgenic mouse model of Alzheimer's disease

Authors: T. NATUNEN[1], ***S. GABBOUJ**[1], H. KOIVISTO[2], S. KEMPPAINEN[1], P. MÄKINEN[1], S. KAIPAINEN[2], M. TAKALO[1], J. LÄMSÄ[2], H. SVOBODOVA[2], H. TANILA[2], M. HILTUNEN[1];
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Abstract: Alzheimer's disease (AD) is the most common form of dementia. Type 2 diabetes (T2D) increases the risk of AD approximately 2-fold. Moreover, alterations in the insulin signaling pathway overlap with molecular pathways relevant to AD pathogenesis. In mice, the typical western diet (TWD) with high fat and sugar content leads to obesity, glucose intolerance and finally full T2D. Here, we studied the effect of TWD on the insulin-Akt-GSK3β pathway in male and female mice with four different AD-linked genetic backgrounds: wild-type (AwTw), APPswe/PS1dE9 (A+), 301Ltau (T+) and double transgenic (A+T+). Mice were fed with TWD or the standard diet (STD) from 5 months of age, underwent behavioral testing at the age of 11-12 months and were sacrificed at 12 months of age. Mice on TWD gained significantly more weight and showed higher fasting and post glucose injection blood glucose levels as compared to mice on STD. Biochemical analysis of hippocampal and cortical samples revealed decreased phosphorylation of Akt1 and Akt2 kinases as well as their downstream kinase GSK3β in mice on TWD. These alterations were most prominent in A+T+ mice. Swim navigation and passive avoidance tests revealed that TWD exacerbated memory impairment due to A or T transgenes. Furthermore, blunted insulin-Akt signaling correlated with impaired spatial learning in the swim test. Our results suggest that TWD leads to impaired insulin-Akt-GSK3β signaling which at least partially explains the detrimental effect of TWD on learning and memory.

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Nanosymposium

189. Neurodegeneration and Injury II

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Presentation Number: 189.02

Topic: C.10. Brain Injury and Trauma

Support: VA Merit Review Grant 5I01RX002335

Title: Voluntary ethanol drinking behavior in an Alzheimer's mouse model following repeated mild traumatic brain injury

Authors: *K. SMITH, S. D. MOORE, R. KLEIN;
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Abstract: Traumatic brain injury (TBI) has been recognized as the “signature injury” of the military, especially in recent military campaigns. Furthermore, evidence suggests that ethanol consumption following injury is associated with poor health outcomes, including increased PTSD symptoms and decreased cognitive processing. Despite this, it is not uncommon for individuals to continue ethanol consumption even after sustaining a TBI, and there is evidence to suggest that TBI may even increase an individual’s risk for ethanol misuse. A sub-population that may be particularly vulnerable to the effects of ethanol on recovery from TBI include carriers of the epsilon 4 allele of the apolipoprotein E (APOE) gene. APOE4 is associated with increased tau pathology characteristic of not only Alzheimer’s disease but also of chronic traumatic encephalopathy (CTE), a neurodegenerative disease resulting from repetitive TBI. Furthermore, evidence suggests that the APOE4 allele confers increased risk of poor cognitive outcomes as a result of ethanol use. To understand the relevance of the APOE4 allele in drinking behavior in the context of TBI, we aimed to establish a model of pre- and post-TBI ethanol consumption in mice expressing either the human APOE3 or APOE4 genotype. We examined voluntary drinking behavior before and after a repeated moderate TBI (rmTBI) paradigm consisting of three closed cortical impacts spaced 24 hours apart. The mice were housed in the automated IntelliCage system, which allow the continuous recording of discrete drinking behaviors in a social context. We report drinking behavior as the percentage of licks each mouse made for ethanol (12%) prior to ethanol withdrawal and when access to ethanol was reintroduced one week post-TBI. We observed that there was a difference in baseline drinking behavior between the genotypes ($F_{(1,22)}$=15.3, p=.0007) with higher consumption in the APOE4 mice (m=28±2.4%,) than in APOE3 (m=6±2.2%). However, there was no main effect of TBI or genotype on drinking behavior ($F_{(3,20)}$=0.7, p=0.56), nor was there any interaction of these two variables either before or after TBI.This preliminary data suggests that there may be underlying alcohol preferences in the APOE4 genotype, but that withdrawal from alcohol may more robustly affect future alcohol preferences than rmTBI. Future behavioral tests are planned to further determine the effect of post-TBI recovery on alcohol seeking behaviors such as motivation and impulsivity.

Disclosures: **K. Smith:** None. **S.D. Moore:** None. **R. Klein:** None.

Nanosymposium

189. Neurodegeneration and Injury II

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Presentation Number: 189.03

Topic: C.10. Brain Injury and Trauma

Support: NICHD Grant R01HD083001
NICHD Grant U54HD087011

Title: Sedative, anesthetic, and alcohol exposure in neonatal mice produces connectomic neuropathology and reductions in functional connectivity

Authors: *K. K. NOGUCHI[1], X. GE[2], M. REISMAN[4], G. KRIKORIAN[2], F. M. MANZELLA[5], S. WILLIAMS[6], J. N. HUFFMAN[7], K. KAPRAL[8], A. BICE[2], B. SWINEY[2], J. P. CULVER[3], J. GARBOW[2];
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Abstract: NMDA antagonists and/or GABA agonists (NAGAs) include numerous drugs that the developing brain may be exposed during medical treatment or as a result of drug abuse (e.g., sedatives, anesthetics, alcohol). Previous animal research has established that developmental NAGA exposure can produce the apoptotic death of millions of neurons resulting in great concern that hundreds of thousands of children may be affected by this pathology each year. Importantly, much of this research has focused on the degeneration of neuronal cell bodies within distinct nuclei, but has largely ignored the connectome - white matter connections between regions. Here we show that alcohol, anesthetics, and sedatives produce an identical pattern of connectome pathology in the corpus callosum, Papez circuit, and pyramidal tract, which is followed by delayed transneuronal degeneration (the death of a healthy neuron following its disconnection from others) in several postsynaptic targets. We also show that neonatal exposure to these drugs produces permanent reductions in brain and measures of white matter volume detected non-invasively in adulthood using magnetic resonance imaging (MRI). Since the destruction of white matter can alter communication between nuclei, we also examined whether neonatal alcohol exposure disrupts functional connectivity (fc) - the temporal correlation of activation occurring between discreet regions in the living brain. In fc optical intrinsic signaling (fcOIS), different colored lights sequentially illuminate the skull to determine regional

activation based on differences in reflectance between oxygenated and deoxygenated hemoglobin. We found that homotopic regions (same region in opposite brain hemispheres) exhibit strong fc in the cortex of controls, but this was reduced in somatosensory cortices of mice exposed to alcohol as neonates. Since neuropathology can alter connectivity, we next analyzed whether the amount of somatosensory fc was correlated with MRI volume measures for each mouse. We found fc was positively correlated with brain and corpus callosum volume, but not other subcortically connected tracts. This significant correlation with fcOIS makes sense, since brain volume is more of a general measure of NAGA pathology and the corpus callosum connects homotopic cortical regions. In summary, this research reveals that NAGAs produce a characteristic pattern of white-matter pathology non-invasively detectable in adulthood that is correlated with reductions in functional connectivity.

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Nanosymposium

189. Neurodegeneration and Injury II

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Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 189.04

Topic: C.10. Brain Injury and Trauma

Support: R35GM131765

Title: Repeated propofol exposure impacts on cortical circuit development and function

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Abstract: Accumulating evidence from animal studies indicates that repeated exposure to general anesthesia during early brain development results in long-lasting behavioral deficits later in life. However, the neuronal circuit mechanisms underlying anesthesia-induced behavioral impairments remain unclear. By performing *in vivo* calcium imaging in the mouse motor cortex, we show a persistent reduction of pyramidal neuron activity after repeated exposure to propofol anesthesia at neonatal ages. The activity of local inhibitory interneuron networks is also altered in adulthood: parvalbumin-expressing interneurons are hypoactive, whereas vasoactive intestinal peptide-expressing interneurons are hyperactive when mice are performing a motor learning task. Administration of pentylenetetrazol to attenuate $GABA_A$ receptor activity or ampakine drug CX546 to potentiate AMPA receptor activity during emergence from anesthesia in mice ameliorates neuronal dysfunction and prevents long-term learning deficits. Together, our results reveal the long-lasting effects of neonatal anesthesia on cortical circuit development and

highlight the prompt restoration of neuronal activity during the post-anesthesia recovery period as an effective strategy to reduce the adverse effects of early-life anesthesia.

Disclosures: H. Zhou: None. **G. Yang:** None.

Nanosymposium

189. Neurodegeneration and Injury II

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Presentation Number: 189.05

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant DP2EB28110

Title: Nanoengineered exosomes drive targeted delivery of reprogramming genes to nerve tissue

Authors: *N. HIGUITA-CASTRO[1], L. LEMMERMAN[1], A. SUNYECZ[1], S. DUARTE-SANMIGUEL[1], M. A. RINCON-BENAVIDES[1], J. T. MOORE[1], G. P. GUIO-VEGA[1], A. I. SALAZAR-PUERTA[1], L. ORTEGA-PINEDA[1], B. DENG[1], H. HARRIS[1], T. NELSON[2], C. L. RINK[1], D. GALLEGO-PEREZ[1];
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Abstract: Gene/oligonucleotide therapy has emerged as a promising strategy for the treatment of a myriad of neurological conditions, including neurodegenerative diseases, brain injury, and cancer. However, current methodologies for delivery to the brain and nerve tissue are fraught with caveats, including reliance on viral vectors, induced toxicity, severe immune/inflammatory responses, and stochasticity. Although adeno-associated viruses (AVV) are less pathogenic, AVV-host interactions and immunity are still a major concern. Moreover, delivery to the CNS is further compounded by the low permeability of the blood brain barrier (BBB). We propose to overcome these barriers by developing nanoengineered exosomes as delivery vehicles for novel therapeutics. Exosome-based therapies for CNS disorders could potentially overcome many of the limitations mentioned above due to their innate ability to penetrate the BBB and deliver cargo to target cells. Moreover, compared to other nanocarrier systems, exosomes show low immunogenicity, especially if derived from the same host, and enhanced stability in biofluids. *In vitro*-derived nanoengineered exosomes loaded with pro-neural factors *ASCL1*, *BRN2*, and *MYT1L* (*ABM*) were isolated after nanoelectroporation of primary mouse embryonic fibroblasts (PMEF). The dynamics of exosome release and uptake was assessed via immunofluorescence microscopy and qRT-PCR in primary cultures of glial cells and neurons. Exosome size and count was analyzed by Nanosight and Transmission Electron Microscopy. Nanoengineered exosome release peaked at 24 hours, with a concentration in the order of billions of particles per milliliter. The number of gene copies packed within the exosomes exceeded the original number of copies delivered to the “donor” cells by 2 -3 orders of magnitude, suggesting intracellular amplification

of the therapeutic cargo. Such exosomes successfully transferred *ABM* gene copies into glial and neuronal cells, and mediated transdifferentiation/maturing. Subsequent studies with exosomes specifically engineered to target foci of injury within the brain indicate that nanoengineered exosomes could conceivably be used to deliver therapeutics to damaged brain tissue in a controlled and targeted manner. Altogether, our findings indicate that nanoengineered exosomes could be used as effective nanocarriers to controllably deliver gene therapies to nerve tissue.

Disclosures: **N. Higuita-Castro:** None. **L. Lemmerman:** None. **A. Sunyecz:** None. **S. Duarte-Sanmiguel:** None. **M.A. Rincon-Benavides:** None. **J.T. Moore:** None. **G.P. Guio-Vega:** None. **A.I. Salazar-Puerta:** None. **L. Ortega-Pineda:** None. **B. Deng:** None. **H. Harris:** None. **T. Nelson:** None. **C.L. Rink:** None. **D. Gallego-Perez:** None.

Nanosymposium

189. Neurodegeneration and Injury II

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Presentation Number: 189.06

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: P60AA011605
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K08AA024829

Title: Extracellular vesicles activate neuroimmune genes, epigenetics and pathology in hippocampus

Authors: *L. G. COLEMAN, Jr[1], J. Y. ZOU[2], F. CREWS[2];
[1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Univ. North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Persistent proinflammatory gene induction is a key feature of several neurologic disorders that may involve epigenetic modification. Extracellular vesicles are emerging as key inter-cellular signaling mediators that carry signaling proteins, mRNAs and microRNAs. Microvesicles (MVs) are extracellular vesicles (0.1-1μm diameter) released from the cell surfaces of somatic cells. We have previously found that MV containing pro-inflammatory HMGB1, IL-1β and other mediators are increased in individuals with Alcohol Use Disorders (AUD). We now report that MVs released after alcohol (i.e. ethanol) exposure induce immune responses in naïve brain tissue, inhibit hippocampal neurogenesis, and induce epigenetic changes in manners consistent with AUD pathology. In order to assess the effect of MVs secreted by

ethanol, hippocampal-entorrhinal cortex (HEC) slice culture was employed. HEC slices were treated with ethanol (100mM) for 4 days, after which media was collected and MVs were isolated by sequential centrifugation. MVs were then added to naïve HEC slice cultures for 4 days, followed by assessment of immune gene induction, neurogenesis, and epigenetic changes in slice tissue. Ethanol-induced MVs activated proinflammatory signaling, inducing TNFα and IL-1β gene expression by 2- and 7-fold respectively. MVs derived from Toll-like Receptors (TLRs 2, 3, 4, 7 and 9) agonist exposure also caused profound induction of TNFα and IL-1β (3-40-fold) in naïve slices. Inhibition of HMGB1 with glycyrrhizin prevented Ethanol-MV induction of TNFα and IL-1β indicating a role for HMGB1 in immune induction by MVs. Ethanol MVs caused a 1.9-fold induction of H3K9 acetylation (gene activation), similar to our findings *in vivo*. Further, ethanol-induced MVs inhibited neurogenesis compared to control-MVs, reducing dentate gyrus doublecortin immunoreactivity by 50%. Ethanol-MVs induced H3K9 histone methyltransferase G9a protein (2-fold) as well its product H3K9me2 (1.5-fold) relative to control-MVs, which is associated with silencing of neuroprogenitor genes. MV signaling represents a novel mechanism of feed-forward immune plasticity, which may contribute to persistent proinflammatory innate immune gene induction through epigenetic mechanisms that contribute to maladaption in addiction and other neuropsychiatric illnesses.

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Nanosymposium

189. Neurodegeneration and Injury II

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Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 189.07

Topic: C.10. Brain Injury and Trauma

Support: CONICYT 74180089

Title: Early low-frequency modulation is related with remnant cognitive processing in disorders of conscious subjects

Authors: *G. RIVERA[1], S. CHENNU[2], T. BEKINSCHTEIN[3], E. STAMATAKIS[3], D. MENON[3];
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Abstract: A significant challenge in the clinical study of disorders of consciousness (DoC) is to ascertain remnant cognitive functions in patients. In these patients, the overt or covert ability to follow commands is considered as an unequivocal sign of awareness, which requires some degree of preserved cognitive functions. Over recent years, mental imagery tasks under functional magnetic resonance imaging (fMRI) have become the research standard for establishing covert awareness in non-communicative brain-injured patients. Alongside, analysis of electroencephalography (EEG) derived measures like connectivity, information theory, and spectral markers have revealed their clinical relevance for detecting such covert cognition. Most of these variables are extracted from spectral features of EEG signals at the delta, theta and alpha bands. However, it is still unknown how the temporal dynamics of the modulation of brain activity in these bands contributes to perceptual processing in DoC patients. To address this gap in knowledge, we combine evidence from fMRI mental imagery task and EEG collected during the global-local stimulus paradigm to identify differences in low-frequency spectral modulation between patients with and without the overt or covert ability to follow commands (CF and N-CF respectively). Data from twenty-four DoC subjects and ten control subjects were analysed. Combining behavioural and fMRI data, fourteen subjects were classified as N-CF and ten were classified as CF. We created a multinomial regression model using elastic net regularization to identify a small number of predictors among EEG spectral variables in the delta, theta and alpha bands to discriminate between N-CF, CF patients and healthy controls. We found that early modulation in the delta band over frontal areas and alpha band over parietal areas were the main discriminators between the three groups. We then carried out a mixed ANOVA to determine whether stimulus complexity produces a differential spectral modulation in these bands. We found evidence that for the three groups, the time window and topographical distribution of spectral modulation depends on stimuli complexity (interaction between Group x Stimuli x time window; $F = 6,7$; $p < 0.001$). Our findings provide evidence that temporal dynamics of the EEG spectrum can contribute to identifying DoC patients with remnant cognitive functions. Taken together, these results highlight the importance of characterising spectral modulation for understanding cognitive processing in DoC.

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Nanosymposium

189. Neurodegeneration and Injury II

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Topic: C.10. Brain Injury and Trauma

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KC16H0230

Title: An epilepsy-associated BK mutation channel modulation by leucine-rich repeat-containing protein LRRC55

Authors: J.-J. WANG[1], X.-M. DONG[1], M. TANG[2], Y. TEN[1], Z. ZHANG[1], ***Q.-Y. TANG**[1]; [1]Jiangsu Province Key Lab. of Anesthesiology, Xuzhou Med. Univ., Xuzhou, China; [2]Dept. of Pathology, the Affiliated Hosp. of Southwest Med. Univ., Luzhou, China

Abstract: Several epilepsy-associated mutations in the pore-forming alfa subunit of the large conductance voltage and calcium-activated potassium (BK, Slo1 or Kca1.1) channel have been identified, some of them show the property of gain-of-function, and some lose-of-function, the underlying mechanisms causing epilepsy remain elusive. Molecular diversity of ion channel function underlies variability in nerve electrical signaling, such as modulation of BK channel by the auxiliary beta subunits. Recently, four types of leucine-rich repeat (LRR)-containing membrane proteins were identified as the auxiliary subunits for BK channel. Among them, LRRC55 shows distinct expression in brain. Here we report that an epilepsy-causing mutation N930S in mSlo1 produced significant shift in BK channel's voltage dependence of activation in the hyperpolarizing direction, especially in the absence or in the presence of low intracellular Ca^{2+} concentration. Furthermore, when co-expression with protein LRRC55, N930S increased BK channel activation rate, and induced a marked left-ward-shift in the BK channel activation. These findings suggest that depending on the expression and distribution of LRRC55 in the brain, the epilepsy mutation co-expressing with LRRC55 increased level of BK channel activation, and may therefore contribute to the pathophysiology of epilepsy.

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Title: Brain volume estimates from clinical MRIs of premature and severely underweight infants acquired in the neonatal ICU may help predict neurodevelopment

Authors: *W. SURENTO[1], I. BA GARI[1], Z. SUN[1], H. KIM[1], P. M. THOMPSON[1], R. CAYABYAB[2], M. SHIROISHI[1], N. JAHANSHAD[1];
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Abstract: Neonatal brain imaging may offer valuable information for predicting neurodevelopmental outcomes in premature infants with very low birth weight (VLBW). They are at high risk for motor impairment and neurodevelopmental disorders such as cerebral palsy. Here we set out to determine whether MRI-derived brain volume measures of preterm neonates better predicted motor performance than simple measures of head circumference and weight at discharge. Preterm neonates (N = 137, F = 66) underwent T2-weighted FLAIR brain scans at the Los Angeles County + USC Medical Center hospital neonatal intensive care unit (NICU) on a 1.5 tesla MRI scanner (voxel dimensions 0.66, 0.66, 4.5 mm) prior to discharge from the NICU. The images were processed using the FSL tool package for initial masking of the brain, which was further refined by neuroanatomical experts. Only the cerebrum, cerebellum, ventricles, and the spinal cord were included in the final T2w image masks. In every subject's final T2w mask, the volume of each voxel was multiplied by the number of voxels to estimate the brain volume (BV) for each subject. At birth, gestational age (GA) ranged from 20.4 to 38 weeks. Neurodevelopmental outcomes for the neonates were assessed with Bayley Scales of Infant and Toddler Development-Third Edition at 6 months corrected age; 70 infants were scored on motor assessments (89.5±19.3). Upon discharge from the neonatal ICU, head circumference (HC) (32.7 ± 3.8 cm) and weight (2773 ± 627 g) of the neonates were measured. BV for the infants was 330.6 ± 58.6 cm3, as estimated by MRI; while the expected BV at term birth is 474.7 cm3 (Wang 2018). Multiple regression tests were performed to test the association between the Bayley motor score and BV, covarying for sex and GA at birth. We compared the motor score association with BV to that of HC and weight at discharge, common standards for assessing infant development growth. We found that BV was positively associated with motor scores ($p=0.025$); neither HC nor weight at discharge were significantly associated with motor scores at 6 months corrected age ($p>0.12$). This suggests that BV, even when calculated from a low-resolution clinical MRI scan, may be a promising biomarker for predicting early neurodevelopmental outcome in VLBW premature infants.

Disclosures: W. Surento: None. **I. Ba Gari:** None. **Z. Sun:** None. **H. Kim:** None. **P.M. Thompson:** None. **R. Cayabyab:** None. **M. Shiroishi:** None. **N. Jahanshad:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.01

Topic: D.03. Somatosensation – Pain

Support: NIDCR K99DE028360
NINDS R35NS105076

Title: Optical analysis of spontaneous nociception

Authors: *D. A. YARMOLINSKY, J. KIM, A. Z. ZHANG, D. G. TAUB, D. P. ROBERSON, B. BOIVIN, C. J. WOOLF;
FM Kirby Neurobio. Ctr., Boston Children's Hosp., Boston, MA

Abstract: Pathological pain states feature both sensitization to environmental stimuli and ongoing pain uncoupled from the external environment. Despite the clinical prevalence and salience of spontaneous pain in neuropathic and inflammatory conditions, it remains unclear how such pain is generated. To address this question, we have developed an experimental platform to allow measurement of neuronal population activity in the spinal dorsal horn, together with quantification of pain-related behaviors in freely moving mice. Chronic optical access to the lumbar spinal dorsal horn is provided by an implanted window fixed to the vertebral column. Utilizing transgenic and viral delivery we target GCaMP sensor expression either to dorsal horn inputs (primary nociceptive neurons) or outputs to brain (lamina I projection neurons). We developed a Miniscope variant suitable for spinal imaging, permitting optical tracking of population activity in freely moving mice over a span of months. In concert with these measurements of neural activity, mice are imaged from below using near-infrared illumination, enabling automated quantification of spontaneous behaviors in a dark and observer-free environment. We are now applying these methods to define spatial and temporal patterns of neural activity associated with expression of spontaneous nociceptive behaviors.

Disclosures: D.A. Yarmolinsky: None. **J. Kim:** None. **A.Z. Zhang:** None. **D.G. Taub:** None. **D.P. Roberson:** None. **B. Boivin:** None. **C.J. Woolf:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.02

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DE026807

Title: Automated pain assessment with millisecond resolution markerless tracking

Authors: J. JONES, ***W. FOSTER**, J. BURDGE, J. PLOTKIN, C. TWOMEY, I. ABDUS-SABOOR;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Behavioral studies in rodents are widely used to uncover the mechanisms governing pain transmission and to develop analgesics that are potent, safe, and specific. However, pain is a highly subjective experience, making simple and objective assessments of rodent pain behavior highly challenging. Here, we record behavior across four inbred mouse strains at 2,000 frames per second and use markerless tracking to construct sub-second behavioral ethograms associated with innocuous and noxious mechanical stimuli applied to the hind paw. Next, using a customized software package, we automatically scored eight distinct movement features across all behavioral trials. We then successfully separated painful from non-painful withdrawal responses using linear discriminant analysis. Additionally, our platform determined that mice with higher anxiety-like levels at baseline showed less intense responses to painful stimuli. This work builds on our manually scored platform (Abdus-Saboor et al., 2019) and demonstrates that combining high-speed videography with automated tracking and scoring reduces time spent manually scoring reflexive pain behavior and minimizes potential human error or bias. The paw withdrawal reflex is the most commonly used assay in preclinical pain research; this platform increases the utility of these studies by quantifying objective behavioral proxies for the sensation an animal is experiencing.
Reference:Ishmail Abdus-Saboor*, Nathan Fried*, Mark Lay, Kathryn Swanson, Justin Burdge, Jessica Jones, Peter Dong, Weihua Cai, Xinying Guo, Yuan-Xiang Tao, Roman Fischer, John Bethea, Minghong Ma, Xinzhong Dong, Long Ding, Wenqin Luo. A mouse pain scale: assessment of pain sensation in mice using sub-second behavioral mapping and statistical modeling.Cell Reports, in press

Disclosures: **J. Jones:** A. Employment/Salary (full or part-time):; The University of Pennsylvania. **W. Foster:** A. Employment/Salary (full or part-time):; The University of Pennsylvania. **J. Burdge:** A. Employment/Salary (full or part-time):; The University of Pennsylvania. **J. Plotkin:** None. **C. Twomey:** None. **I. Abdus-Saboor:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.03

Topic: D.03. Somatosensation – Pain

Support: CIHR FDN-154336
UTCSP Pain Scientist Scholarship

Title: Antibiotic treatment does not influence basal nociception or pain hypersensitivity after injury

Authors: *K. HALIEVSKI, T. H. TAM, M. DRUPALS, M. W. SALTER;
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Abstract: Chronic pain affects 20% of the population but effective treatments are lacking. Individual variation contributes greatly to how one experiences pain and understanding variability may lead to tailored and efficacious treatments for specific people. To explore whether the microbiota affects acute nociception or hypersensitivity following painful injury, we subjected male (M) and female (F) C57Bl6 mice to broad-spectrum oral antibiotics (ABX; ampicillin, neomycin, vancomycin, erythromycin, and gentamycin) for three weeks prior to either a hindpaw incision (n=12/sex/treatment) or a spared nerve injury (SNI; n=4-5/sex/treatment). We validated depletion of the gut microbiome with the presence of a grossly enlarged caecum in each ABX-treated mouse. We used nociceptive behavioural tests: mechanical sensitivity, dynamic weight bearing, and thermal place preference. Statistical analysis was done using mixed-design ANOVA and T-tests as appropriate. Three weeks of ABX treatment had no statistically significant effect in either sex, compared with vehicle controls, on baseline mechanical or thermal sensitivity. After injury, mechanical withdrawal thresholds were reduced compared to baseline in animals receiving incision or SNI. We found that treatment with ABX had no effect on the development of mechanical hypersensitivity after incision (ABX*Injury: M, p=0.411; F, p=0.569), nor did treatment influence the overall course of hypersensitivity (area under the curve (AUC): M, p=0.174; F, p=0.867). Likewise, ABX had no effect on mechanical hypersensitivity following SNI (ABX*Injury: M, p=0.987; F, p=0.731; AUC: M, p=0.703; F, p=0.682). On the dynamic weight bearing assay, we did not detect any differences in left (injured) - right (uninjured) distribution between vehicle- and ABX-treated groups after incision (M, p=0.520; F, p=0.566) or after SNI (M, p=0.744; F, p=0.203). Thermal hypersensitivity also did not differ between vehicle- and ABX-treated mice after incision (M [ABX*Injury, p=0.325; ABX, p=0.262] F, [ABX*Injury, p=0.430; ABX: p=0.532]) or SNI (M [ABX*Injury, p=0.706; ABX: p=0.285], F [ABX*Injury, p=0.476; ABX: p=0.914]). In sum, we found that long-term ABX treatment did not affect behavioural responses in acute nociception or in injury-induced hypersensitivity.

Disclosures: K. Halievski: None. **T.H. Tam:** None. **M. Drupals:** None. **M.W. Salter:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.04

Topic: D.04. Somatosensation – Touch

Support: NIH R01 102978
NIH R01 104742

Title: Altered adaptation and gain in sensory circuits of the casein kinase 1 delta (CK1δ) mouse model of migraine

Authors: *P. S. SURYAVANSHI, P. SAWANT-POKAM, J. GAYNES, K. BRENNAN; Univ. of Utah, Salt Lake City, UT

Abstract: Migraine is a very common and disabling neurological disorder that remains poorly understood at the cellular and circuit level. Transgenic mice harboring a human mutation in casein kinase 1 delta (CK1δ T44A) represent the first animal model of monogenic non-hemiplegic migraine. These mice have decreased sensory thresholds to mechanical and thermal pain after treatment with the migraine trigger nitroglycerin; and an increased susceptibility to cortical spreading depression (CSD), which models the migraine aura. In this study, we investigated cellular and synaptic mechanisms within sensory cortical circuits that might underlie the migraine relevant phenotypes of CK1δ mice, using *in vitro* and *in vivo* whole cell electrophysiology as well as 2-photon microscopy. Surprisingly we found that at resting state, CK1δ neurons exhibited hyperpolarized membrane potentials, due to increased tonic inhibition, as well as membrane resistance similar to wild type neurons. Moreover, spontaneous synaptic as well as dendritic currents were also found to be similar between the two genotypes. Despite this reduction in baseline excitability, CK1δ neurons fired more frequent action potentials in response to current injection. And despite similar synaptic and dendritic characteristics to wild type neurons, excitatory but not inhibitory CK1δ synapses failed to adapt to high frequency short-stimulus trains, resulting in higher steady state excitatory currents. These in turn were a result of an increased replenishment rate of the readily releasable pool, providing a presynaptic mechanism for the CK1δ phenotype. During *in vivo* experiments, CK1δ animals showed increased duration and membrane potential variance at 'cortical up states'; showing that the intrinsic and synaptic changes we observed have excitatory consequences at the local network level. On a translational level, CK1δ neurons had higher calcium load during CSD measured using 2-photon microscopy. In conclusion, excitatory sensory cortical neurons and networks in CK1δ animals appear to exhibit stimulus intensity dependent impaired adaptation and increased gain, likely due to pre-synaptic mechanisms.

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Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.05

Topic: D.02. Somatosensation

Support: BBSRC N006119/1
WT 102645

Title: Expression of neuropeptide FF by neurons in mouse spinal dorsal horn

Authors: *M. GUTIÉRREZ MECINAS, A. M. BELL, E. POLGAR, A. J. TODD;
Inst. of Neurosci. and Psychology, Univ. of Glasgow, Glasgow, United Kingdom

Abstract: The superficial dorsal horn (SDH) of the spinal cord contains the first relay for nociceptive and pruritoceptive primary afferents. The vast majority of cells in this area are interneurons, and these are diverse in their structure and function. They are organized into complex circuits, which are not yet completely understood. In lamina I-II of the spinal cord, excitatory interneurons account for around three quarters of all neurons. During the last few years we have identified five non-overlapping populations. Four of these are defined by expression of substance P, neurokinin B, neurotensin and cholecystokinin, and the fifth by expression of green fluorescent protein (GFP) in a gastrin-releasing peptide (GRP)-GFP mouse line. These populations generally match clusters described by Haring et al (2018) using transcriptomics. Another cluster defined by transcriptomics consists of cells that express neuropeptide FF (NPFF). In this study we aimed to identify and characterize the NPFF cells in the mouse SDH . We found that cells immunolabelled with a pro-NPFF antibody account for around 5% of neurons in SDH and all of them are excitatory interneurons. Using both, immunocytochemistry and *in situ* hybridization, we found out that NPFF cells were different from the 5 populations described above. We also examined phosphorylation of extracellular signal-regulated kinases to investigate their responses to noxious (pinch, heat, capsaicin) and pruritic (chloroquine, histamine) stimuli. Some of the NPFF cells responded to each of these stimuli: around a third to pruritic stimuli and noxious heat, and around half to pinch and capsaicin.
These results suggests that NPFF cells represent a discrete functional population among the excitatory interneurons in the SDH.

Disclosures: M. Gutiérrez Mecinas: None. **A.M. Bell:** None. **E. Polgar:** None. **A.J. Todd:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.06

Topic: D.03. Somatosensation – Pain

Support: WBS R-581-000-147-133

Title: Exploring the peripheral and central contributions to offset analgesia with stimulus placement and timing

Authors: *S. W. G. DERBYSHIRE[1], C. L. ASPLUND[2], V. J. E. LONG[2], A. KANNANGATH[2];

[1]Psychology, Natl. Univ. Of Singapore, Singapore, Singapore; [2]Yale-NUS Col., Singapore, Singapore

Abstract: A noxious stimulus following a more intense stimulus often feels less painful than a continuous noxious stimulus (Grill & Coghill, 2002). This effect, known as offset analgesia (OA), may be due to descending inhibitory control (Derbyshire & Osborn, 2009), to changes in peripheral neural transmission (Ligato et al., 2018), or both. We designed a series of experiments to examine whether OA is altered by the placement and timing of noxious thermal stimulation to potentially reveal peripheral or central mechanisms. Three separate studies were conducted using offset, constant and baseline trials. The first study (N=21) delivered stimuli to the right hand, left hand and left calf. Offset trials included a 45 °C (T1, 6 s) stimulus, followed by a 1 °C further increase (T2, 6 s) and then a 1 °C decrease (T3, 12 s) back to 45 °C. Baseline trials were the same except at T3 the temperature returned to 35 °C. Constant trials continued at 45 °C throughout T1, T2 and T3. Subjects continuously rated pain intensity using a sliding scale. The second study (N=29) delivered stimuli to the back and the palm of the right hand using 1 or 6s time periods for T1 and T2. The third study (N=48) delivered stimuli to the left and right forearms with varying T1 and T2 durations (3, 6, 10 or 13s) and a 20s T3 period. For both studies two and three, the noxious temperatures were 1°C lower compared to the first study. Study one revealed an equivalent offset effect for the hands and the left leg. By contrast, the 6s stimulus periods in study two generated OA on the back of the hand but not on the palm. No effects were found with 1s durations at either location. Study three also found no OA with 3s duration stimuli. The OA effect was marginal at 6s, however, and strong at 10s and 13s. In general, across the range of stimulus durations used, OA effects became stronger with longer duration stimulus periods. This finding implies that a rapid decrease in Type II AMH fiber firing is not responsible for OA effects. These effects were noticeably attenuated on the palm, however, which does imply a relatively important role for Type II AMH fibers in OA (Naugle et al., 2013). The increasing OA effects with longer duration stimuli suggest that accumulated signalling evokes top-down analgesia or accumulated peripheral habituation causes such analgesia. We conclude that combined effects may produce the OA effect or that either peripheral or top-down influences dominate in different OA experimental paradigms.

Disclosures: S.W.G. Derbyshire: None. **C.L. Asplund:** None. **V.J.E. Long:** None. **A. Kannangath:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.07

Topic: B.06. Synaptic Transmission

Support: NIH 3OT2OD025307-01S1

Title: Consequences of infrared neuromodulation to the transcriptome of the nodose ganglia

Authors: *S. JAWAID[1], S. MEHTA[6], P. M. GETSY[2], G. A. COFFEE[3], L. THRANE[4], J. ZHUO[4], S. J. LEWIS[5], M. WATANABE[5], M. W. JENKINS[4];
[1]Biomed. Engin. and Pediatrics, [2]Pediatrics Pulmonology, [3]Pediatric Pulmonology, [4]Dept. of Pediatrics & Biomed. Engin., [5]Dept. of Pediatrics, Case Western Reserve Univ., Cleveland, OH; [6]Yale Ctr. for Genome Analysis, Yale Univ., New Haven, CT

Abstract: Neuromodulation of peripheral ganglia is a novel strategy to elicit cardiorespiratory responses and to better understand and control peripheral nervous system functions. Infrared neuromodulation (IRN) is one such promising methodology with high spatial precision and preferential selectivity for small-diameter fibers. We found that application of IRN to the rat nodose ganglia (NGs) elicits spatially distinct patterns of cardiorespiratory responses. NGs contain cell bodies of vagal afferents from the heart, lungs, intestines and other organs and sends projections to many structures including the brain. The aim of the current study was to identify changes in gene expression in rat NGs following IRN in order to reach a deeper understanding of the effects of IRN on neural activity and cellular processes, potential therapeutic targets and possible negative effects that would guide us towards effective and safe IRN parameters. Male Sprague-Dawley rats (P25) were anesthetized with an i.p. injection of Ketamine (100 mg/kg) + Xylazine (10 mg/kg) and either the left or right NGs were exposed to IR for 20 secs using a 400 µm diameter fiber placed directly on the NG (1443 nm; 0.37 J/cm^2/pulse; 200 µs pulse length; 200 pulses/s). After 6 hours of recovery, rats were reanesthetized and both the IR exposed and contralateral unexposed ganglia were flash frozen in liquid nitrogen. RNAs were extracted using an RNeasy Plus Micro Kit (Qiagen) and sequenced on an Illumina HiSeq 2500 (rapid run mode 2x75). Our initial transcriptome and statistical analyses identified 106 genes exhibiting significant differential expression (DE, p-value <0.05 and >1.6-fold change, both up- and down-regulated) when comparing IR exposed NGs to unexposed NGs. For example, Piezo1, Hspa1a, Serpine1, S100a9, Gfap, Fos were upregulated and Stoml1, Slc35b2, Glrx2, Elp5 were down-regulated. Intriguingly, our results indicate that unexposed NGs have changes in gene expression induced by IR treatment of the contralateral NG suggesting that the left and right ganglia are functionally connected. We further analyzed cell type specificity (astrocytes, microglia, neurons, oligodendrocytes and endothelial) for the genes with significant DE and identified key pathways significantly altered in the IR exposed NGs. Our RNA-Seq data and graphical representations show promising leads in the identification of molecules and pathways revealing the mechanism of IRN in NGs. Our overall goal is to create and apply new tools that will control autonomic ganglia and visualize activity within them. This will lead to a deeper understanding of how they function and the development of new treatments for prevalent diseases.

Disclosures: S. Jawaid: None. **S. Mehta:** None. **P.M. Getsy:** None. **G.A. Coffee:** None. **L. Thrane:** None. **J. Zhuo:** None. **S.J. Lewis:** None. **M. Watanabe:** None. **M.W. Jenkins:** None.

Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 190.08

Topic: D.02. Somatosensation

Support: HHMI
NINDS R35
Alice and Joseph Brooks Fund Postdoctoral Fellowship
Blavatnik Biomedical Accelerator Grant

Title: Genetic dissection of ascending spinal pathways for affective touch and pain

Authors: *S. CHOI[1], J. HACHISUKA[2], M. A. BRETT[1], H. R. KOERBER[2], S. E. ROSS[2], D. D. GINTY[1];
[1]Neurobio., Harvard Med. School/HHMI, Boston, MA; [2]Neurobio., Univ. of Pittsburgh/Pittsburgh Ctr. for Pain Res., Pittsburgh, PA

Abstract: The anterolateral system consists of tracts that ascend within the anterior and lateral part of the spinal cord white matter and conveys touch, pain, and temperature information from the periphery to multiple regions in the brain. The spinoparabrachial (SPB) tract terminates in the lateral parabrachial nucleus (PBN_L) of the pons, a main brain target of the anterolateral system that relays multimodal sensory signals to higher brain centers. The projection neurons in the anterolateral system, including SPB neurons, are attractive therapeutic targets for pain treatment because nociceptive signals emanating from the periphery channel through these spinal projection neurons. However, the subdivisions and organizational logic of the anterolateral pathway are poorly understood. Here we show that two projection neuron populations that express structurally related GPCRs, NK1R (Neurokinin 1 receptor) and GPR83, form parallel ascending circuit modules that are anatomically, physiologically, and functionally distinct. We found that GPR83-expressing SPB neurons are uniquely sensitive to cutaneous mechanical stimulation and receive strong synaptic inputs from both high- and low-threshold primary mechanosensory neurons. Remarkably, the axons of the NK1R- and GPR83-expressing SPB neurons terminate in a partially-segregated manner within the PBN_L, and optogenetic stimulation of the axon terminals of these two neuronal populations induces distinct patterns of escape locomotion and autonomic responses. Moreover, while activation of NK1R-expressing SPB neurons elicits aversive behavioral responses, the valence associated with activation of GPR83-expressing SPB neurons is either positive or negative depending on stimulus intensity; low-intensity stimulation is appetitive whereas high-intensity stimulation is aversive. Overall, our findings support a model in which the PBN_L receives touch, pain, and temperature information from physiologically and anatomically distinct SPB circuit motifs and broadcasts somatosensory signals to other brain regions to generate proper behavioral responses to changes in the physical world.

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Nanosymposium

190. Pain and Itch Behavior, Circuitry, and Novel Techniques

Location: Room S106

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Presentation Number: 190.09

Topic: D.02. Somatosensation

Support: startup funds to B.D. from the Department of MCDB and Neuroscience Scholar Program, University of Michigan

Title: Encoding the mechanical itch circuit: From the periphery to the spinal cord

Authors: H. PAN[1], ***M. FATIMA**[1], A. LI[1], H. LEE[1], W. CAI[2], N. ZAHER[1], C. C. HUR[1], L. R. HORWITZ[1], M. CIN[1], H. SLADE[1], T. HUANG[3], X. XU[2], B. DUAN[1];
[1]Dept. of Molecular, Cell. and Developmental Biol., [2]Life Sci. Inst., Univ. of Michigan, Ann Arbor, MI; [3]Dana-Farber Cancer Institute, Harvard Med. Scho, Boston, MA

Abstract: An innocuous tactile stimuli when perceived by the skin can induce the sensation of itch. Much progress has been made in dissecting the sensory neuronal networks for chemical itch transmission. However, a complete understanding of the neural circuits that process mechanical itch is still lacking. We identified a subpopulation of Ucn3+ interneuron in the dorsal spinal cord as a key spinal component required for the transmission of mechanical itch, and mechanical itch sensitization as well as persistent spontaneous itch in chronic itch conditions. Spinal Ucn3+ neurons population receives afferent inputs from Toll-like receptor 5-positive (TLR5+) Aβ mechanoreceptors, and is directly innervated by inhibitory interneurons expressing neuropeptide Y::Cre (NPY+) in the dorsal spinal cord. Decreased NPY-imposed synaptic inhibition and enhanced intrinsic excitability of Ucn3+ neurons are essential for the transition from acute to chronic itch. Our study sheds new light on the neural mechanisms of chronic itch and offers avenues for developing therapeutic approaches.

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Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 191.01

Topic: D.07. Vision

Support: 1R01EY027402-02
5T32 EY007135-23
Whitehall Foundation
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Alfred P. Sloan Foundation

Title: Neural mechanisms of binocular convergence in the primate primary visual pathway

Authors: *K. DOUGHERTY[1], B. M. CARLSON[1], M. A. COX[2], J. A. WESTERBERG[1], M. S. SCHALL[1], J. N. TURCHI[3], P. R. MARTIN[4], A. V. MAIER[1];
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Abstract: The primate brain combines the signals from the two eyes to yield a singular view of the world. By combining binocular inputs, primates gain stereopsis, hyperacuity, as well as other forms of improved visual performance. The exact meeting point of the two eyes' outputs in the primary visual pathway is unclear. The first possible meeting point is the lateral geniculate nucleus (LGN) of the thalamus. Retinal ganglion cells innervate mutually exclusive groups of neurons in this structure, and almost all LGN neurons respond to stimulation of one eye but not the other. Yet, there is both anatomical and physiological evidence suggesting that some LGN neurons modulate their response when both eyes are stimulated simultaneously (binocular modulation). At the next step in the visual hierarchy, the primary visual cortex (V1), most neurons respond to either eye. Nonetheless, there is a small fraction of V1 neurons, particularly among those in the primary LGN input layer (layer 4), that respond to one eye only. Just like those in the LGN, layer 4 monocular V1 neurons may modulate under binocular viewing—another possible meeting point of the two eyes' signals. Taken together, the two eyes' signals may initially interact 1) in the LGN, 2) in the primary input layer 4 of V1, or 3) beyond layer 4 of V1. In this study, we tested these alternative hypotheses by recording from neurons in the LGN ($n > 60$) and neurons across the layers of V1 ($n = 138$) using linear multicontact electrode arrays in awake, behaving macaques. We stimulated neurons' receptive fields with sine-wave gratings that were presented to one eye, the other eye or in matching positions of both eyes. Approximately one-fifth of LGN neurons showed significant modulation under binocular stimulation. Using reversible pharmacological inactivation of V1, we are aiming to precisely locate the neural origin of this binocular modulation. Unlike the LGN, almost all neurons in V1, including the monocular neurons responding to only one eye, significantly modulated their responses during binocular viewing. Overall, the majority of initial binocular interactions in the primate visual system seem to occur within V1, including the layer receiving direct geniculate input.

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Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

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Presentation Number: 191.02

Topic: D.07. Vision

Support: Research Leadership Award RL-2012-019 from the Leverhulme Trust to JR

Title: Seeing in 3D without a cortex - Neurons for stereopsis in an insect brain

Authors: ***R. ROSNER**[1], G. TARAWNEH[1], V. NITYANANDA[1], J. VON HADELN[2], J. READ[1];
[1]Inst. of Neurosci., Newcastle Univ., Newcastle upon Tyne, United Kingdom; [2]Philipps-University Marburg, Marburg, Germany

Abstract: The praying mantis is the only invertebrate known to possess stereoscopic vision (stereopsis), the capability of seeing in depth by employing binocular vision.[1,2] Mantids are predatory insects which determine whether prey is in catching range by exploiting the slightly shifted images both eyes see of the same region in space. The neuronal basis of mantis stereopsis was enigmatic for more than 30 years. By employing a virtual environment for presenting visual stimuli in 3D combined with intracellular neuronal recordings we discovered a range of neurons in the praying mantis brain which are tuned to specific distances and azimuths in 3D space.[3]
In behavioural experiments we presented a moving disc, which mimicked prey, to seemingly float in front of a 3D computer screen. Mantids eagerly strike at the disc with their raptorial front legs when the disc seems in catching range but not otherwise.[1] Then we presented the disc to mantids which were immobilized in front of the screen. While the animals were presented with the stimulus we recorded in the animal's brain with sharp electrodes. Then we stained the neurons and determined their morphology. We discovered neurons that responded vigorously to a disc floating in front of the screen and we mapped the 3D receptive fields of these cells. Here we show that specific neuron types in the praying mantis brain are tuned to locations in 3D space. These types comprise projection neurons which link the optic lobes with the central brain, commissural neurons which link both optic lobes and, surprisingly, also feedback connections (centrifugal neurons) which project from the central brain to early visual processing centres in the optic lobes. Such stereoscopic feedback has not yet even been shown in vertebrates. The response properties of the discovered mantis neurons are reminiscent of neurons in the visual cortex of primates. Mantis stereopsis opens a testbed for further studies on the implementation of stereoscopic vision in a comparatively simple brain with potential implications for more efficient algorithms in machine vision.

1. Nityananda V, Tarawneh G, Rosner R, Nicolas J, Crichton S, Read J. Insect stereopsis demonstrated using a 3D insect cinema. Sci Rep. 2016;6:18718.
2. Rossel S. Binocular stereopsis in an insect. Nature. 1983;302(5911):821-822.
3. Rosner R, von Hadeln J, Tarawneh G, Read J. The neuronal basis of insect stereopsis. bioRxiv. 2018:395939.

Disclosures: **R. Rosner:** None. **G. Tarawneh:** None. **V. Nityananda:** None. **J. von Hadeln:** None. **J. Read:** None.

Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 191.03

Topic: D.07. Vision

Support: NIH Grant U01NS094330
NIH Grant EY025102
Human Frontier Science Program Grant

Title: Mice discriminate stereoscopic surfaces without fixating in depth

Authors: *J. M. SAMONDS, V. CHOI, N. J. PRIEBE;
Neurosci., Univ. of Texas at Austin, Austin, TX

Abstract: Stereopsis is a ubiquitous feature of primate mammalian vision, but little is known about if and how rodents, such as mice, use stereoscopic vision. We used random dot stereograms to test for stereopsis in mice and they were able to discriminate near from far depths over a range of disparities with diminishing performance for small and large binocular disparities. Based on two-photon measurements of disparity tuning, the range of disparities represented in the visual cortex aligns with the behavior and covers a broad range of disparities. When we examined their binocular eye movements, we found that mice did not systematically vary eye alignment, or use vergence eye movements, when presented with different disparities like primates. Nonetheless, the representation of disparity tuning is wide enough to capture stereoscopic information over a range of potential alignments. Although mice share fundamental characteristics of stereoscopic vision with primates and carnivores, their lack of disparity-dependent vergence eye movements and wide neuronal representation suggests that they may employ a distinct strategy for stereopsis.

Disclosures: **J.M. Samonds:** None. **V. Choi:** None. **N.J. Priebe:** None.

Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 191.04

Topic: D.07. Vision

Support: NIH Grant EY014999

Title: Perfect optical correction reveals visual plasticity driven by the retinal image quality

Authors: *C. J. NG[1], D. TADIN[2], R. BLAKE[3], M. S. BANKS[4], G. YOON[1];
[1]Flaum Eye Inst., [2]Ctr. of Visual Sci., Univ. of Rochester, Rochester, NY; [3]Psychology, Vanderbilt Univ., Nashville, TN; [4]Optometry, Univ. of California Berkeley, Berkeley, CA

Abstract: Visual perception depends on the quality of optical images formed on the retina and on subsequent neural processes. Using adaptive optics (AO) to bypass human optics, we isolated neural contributions to visual perception. This allowed us to reveal how long-term adaptation to optical imperfections changed cortical processing of visual information, here focusing on spatial phase perception, binocular contrast summation and stereopsis. Performance was measured with full optical correction in real-time using a binocular AO vision simulator. We tested three participants with normal optics and two with keratoconus - a condition where people with normally developed visual systems have severe optical imperfections in adulthood. Spatial phase perception was measured monocularly using supra-threshold compound gratings (2 and 4cpd) added in various phases; participants indicated the phase where the stimulus appeared perceptually balanced. Contrast sensitivity was measured at 2 and 4cpd monocularly and binocularly, with the benefit of binocular viewing quantified by the ratio of binocular to monocular sensitivity. Stereo sensitivity was measured using sinusoidal depth corrugations. Improvement was quantified by the ratio of sensitivities at full optical correction divided by sensitivity under normal viewing. We found that keratoconus had a significant effect on perceived spatial phase relative to normal (mean difference of 12.4°; p=0.02). Keratoconics also had lower contrast sensitivity (by 21.5% monocularly, p=0.07; 33.7% binocularly, p=0.08). Across participants, binocular benefit was 1.4-2 while the interocular difference in phase perception was 1.7-11.8°, the two measures being negatively correlated (r=-0.76). Stereo-sensitivity improved with perfect optics (0.037 vs. 0.022 arcsec-1; p=0.05), and this improvement was negatively correlated with the interocular difference in habitual optical quality (r=-0.86). Our phase results show that perfecting the retinal image did not yield veridical perception; rather it revealed perceptual distortions caused by neural processing. Likewise, subjects with larger interocular difference in optical quality should show greater binocular benefit from full correction. Instead, binocular improvements were negatively correlated. These results suggest that the cortex adapts to optical imperfections, compensating for the retinal image quality to promote more nearly veridical perception under natural viewing conditions.

Disclosures: **C.J. Ng:** None. **D. Tadin:** None. **R. Blake:** None. **M.S. Banks:** None. **G. Yoon:** None.

Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

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Topic: D.07. Vision

Support: NIH Grant EY10217
NIH Grant EY02162
Research to Prevent Blindness

Title: Binocular interactions in V1 neurons of awake macaques raised with strabismus

Authors: *D. L. ADAMS, J. R. ECONOMIDES, J. C. HORTON;
Beckman Vision Ctr., UCSF, San Francisco, CA

Abstract: Children with strabismus acquired early in life do not experience diplopia. To investigate how perception of the duplicate image is suppressed, we recorded from V1 in 2 monkeys with divergent strabismus. At age 4 weeks the medial rectus muscle in each eye was disinserted to induce an alternating exotropia without amblyopia. Once the animal was old enough for testing, a headpost and recording chamber were implanted for daily recordings from the right striate cortex using quartz glass Pt/W tetrodes. Stimuli were rear-projected onto a large tangent screen and each eye's position was monitored independently with video eye trackers. After a cell was isolated the locations of the receptive fields were mapped. The cell was then stimulated under 8 interleaved conditions: left eye's field, right eye's field, or both eyes' fields with either right eye fixating or left eye fixating, plus left eye occluded and right eye occluded. The animal's task was to foveate a small spot placed a distance of half the ocular deviation either to the right or left of the screen center. This enabled switches in fixation between right and left eye with little change in the eyes' orbital positions. Once the fixation spot was acquired for 250 ms by the appropriate eye, a drifting grating(s) moving in 1 of 8 directions was presented for 250 ms within the receptive field(s), followed by another 250 ms epoch with only the fixation spot. The monkey was rewarded for maintaining fixation the entire 750 ms period. We recorded 147 cells in monkey 1 and 80 cells in monkey 2, with similar results. As expected, ocular dominance histograms showed a monocular bias compared with normal animals, but many cells still remained responsive to both eyes. Eye of fixation's impact was tested by two comparisons: 1) responses to binocular stimulation during right eye versus left eye fixation trials, 2) responses to monocular stimulation of a given eye during right eye versus left eye fixation trials. Few cells showed any marked effect, by either test. Interocular suppression was assessed by three comparisons: 1) responses to stimulation with one eye occluded versus binocular stimulation, 2)

responses to stimulation with one eye occluded versus monocular stimulation of the same eye with both eyes open, 3) responses to monocular stimulation with both eyes open versus binocular stimulation. Surprisingly, the majority of cells showed little evidence of either suppression or enhancement. These data indicate that extrafoveal cells in V1 of exotropic animals do not modulate their firing rate with changes in eye of fixation or demonstrate interocular suppression. Elimination of diplopia is therefore likely to be mediated at a higher cortical level.

Disclosures: D.L. Adams: None. **J.R. Economides:** None. **J.C. Horton:** None.

Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

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Topic: D.07. Vision

Support: NIH DP2 grant NEI EY024504
Knights Templar Eye Foundation Grants
Canadian Institutes of Health Research Postdoctoral Fellowship

Title: Critical-period monocular deprivation disrupts binocular integration in the mouse thalamocortical circuit

Authors: *C. HUH[1], K. ABDELAAL[1], K. J. SALINAS[1], D. GU[1], J. ZEITOUN[1], D. X. FIGUEROA VELEZ[1], J. P. PEACH[2], C. C. FOWLKES[1], S. P. GANDHI[1];
[1]Univ. of California, Irvine, Irvine, CA; [2]Johns Hopkins Univ., Baltimore, MD

Abstract: The study of experience-dependent sculpting of binocular circuits has largely focused on primary visual cortex (V1). However, recent evidence suggests that neurons in dorsolateral geniculate nucleus of the thalamus (dLGN) are significantly modulated by binocular vision. Moreover, monocular deprivation (MD) has been shown to unmask substantial binocular processing in dLGN. Using *in vivo* two-photon Ca^{2+} imaging of dLGN afferents in mouse V1, we demonstrate that, contrary to previous reports that tested acute effects of MD, long-term (14-day) MD during the critical period leads to a chronic loss of binocular dLGN inputs. MD also leads to profoundly mismatched visual tuning properties in surviving binocular inputs. Furthermore, MD was found to impact modulation of dLGN inputs during binocular viewing. Our data show that critical-period MD produces long-lasting disruptions in thalamic binocular integration and suggest that the development of normal binocular vision may depend upon experience-dependent refinement of binocular circuits in the thalamus. This discovery sheds new light on the potential role for thalamic deficits in developmental disorders of the central visual system such as amblyopia.

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Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 191.07

Topic: D.07. Vision

Title: Altered interocular balance following STMD revealed by gamma band activity

Authors: *R. A. MILLER, III[1], D. Y. TS'O[2];
[1]SUNY Upstate Med. Univ., Syracuse, NY; [2]Dept of Neurosurg., SUNY - Upstate Med. Univ., Syracuse, NY

Abstract: Interocular balance, the appropriate weighting of left and right eye neural signals, is an important prerequisite for achieving the advantages of binocular vision. An altered interocular balance has been demonstrated experimentally in humans and animals following a short term (1-2 hours)monocular deprivation (STMD). The primary reported outcome is a relative increase in the deprived eye (DE) gain post-deprivation, which may last up to 90 minutes. The neural origin of this effect has yet to be elucidated.Before, during and after a 1-2 hour monocular deprivation in adult macaque monkeys, intracortical V1 responses were recorded using a 16 channel linear multielectrode array. The spectral power of gamma band (25-60Hz) activity derived from the local field potential (LFP) was quantified at each presentation of oriented grating stimuli. Following STMD, the deprived eye responses were observed to be relatively greater than the non-deprived eye (NDE) responses. This shift in interocular balance was primarily due to a significantly weakened NDE response during the monocular deprivation. At times the NDE response did not return to its pre-deprivation level until up to an hour after balanced binocular stimulation had been restored. This gamma-band activity measurement may correspond to the previously reported relative DE perceptual gain following STMD, as well as similar V1 optical imaging results. In comparison to V1 single unit data recorded under these STMD conditions,the LFP measurement has proven more robust at demonstrating the STMD-induced shifts in interocular balance. The findings suggest that the apparent relative increased DE gain may be attributed to deprivation-induced NDE suppression.

Disclosures: **R.A. Miller:** None. **D.Y. Ts'o:** None.

Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 191.08

Topic: D.07. Vision

Title: Interocular contrast mismatch leads to shifts in interocular balance

Authors: *D. Y. TS'O, R. A. MILLER, III;
Neurosurg., SUNY - Upstate Med. Univ., Syracuse, NY

Abstract: Interocular imbalance may be created by the presentation of fusable stimuli dichoptically with each eye receiving differing contrast. An extreme variant of this paradigm, monocular deprivation (STMD), carried out over 1-3 hours, induces a surprising temporary shift in interocular balance wherein the deprived eye (DE) gets relatively stronger post-deprivation in comparison to the non-deprived eye. To determine the generality and symmetry of this STMD effect with interocular contrast imbalance, optical imaging of primate V1 for ocular dominance columns (ODCs) was conducted during 1-2 hour periods of presenting matching and mismatched interocular contrast. The sessions started with a baseline of 40% contrast sine gratings of four orientation to each eye. Then the left (manipulated) eye (ME) was switched to 80% contrast, back to 40%, then to 20%, then back to 40% while the right eye was constantly stimulated with 40% (each period lasted for 1-2 hours). Line profiles across the ODCs show DC offset shifts indicative of the relative strength of each eye's response. The result is that immediately after the contrast imbalance begins, the response to the ME stimuli is commensurate with the new mismatched contrast, but later the response begins to shift to match the fellow eye. Whenever the ME returns to baseline (40%), the response "overshoots" or "undershoots" DC zero implying a relative gain change that opposes the previous contrast imbalance. An additional analysis that examines the peak-peak amplitude of the ODC signal shows a similar result. This behavior indicates a binocularly-regulated interocular balancing mechanism, with a time constant of ~30mins. Although this STMD gain shift effect was approximately symmetrical, there was an asymmetry such that the 40-80% increment yielded a larger gain shift than the 40-20% decrement.
Preliminary V1 multi-electrode array local field potential recordings before, during and after 1-2 hours of interocular contrast mismatch also demonstrates a gradual increase in the response of the deprived (lower contrast) eye over time, again supporting the notion of a binocular homeostatic mechanism regulating interocular balance.

Disclosures: D.Y. Ts'o: None. **R.A. Miller:** None.

Nanosymposium

191. Neuronal Circuits Underlying Binocular Vision and Stereopsis

Location: Room S505

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 191.09

Topic: D.07. Vision

Support: R01 EY026156
NIH Eureka Grant

Title: Synergistic coding of visual information in columnar networks

Authors: *S. NIGAM, S. POJOGA, V. DRAGOI;
Dept. of Neurobio. & Anat., McGovern Med. Sch., Houston, TX

Abstract: Stimuli in the environment are encoded collectively by the activity of populations of cortical neurons. These populations transmit information to downstream areas by using a neural code that is thought to be predominantly redundant. Redundant coding is widely believed to reflect a design choice by which cortical neurons with overlapping receptive fields sample each stimulus in the environment to convey similar information. Here, we reexamined the idea of redundant coding by performing multi-electrode laminar recordings in awake monkey primary visual cortex (V1). Contrary to previous work we find significant synergy in pairs, triplets and quadruplets of neurons. Roughly 40% of pairs, triplets and quadruplets in cortical columns exhibit synergistic interactions. These interactions are clustered non-randomly across cortical layers to form synergy and redundancy hubs. Synergy hubs interact synergistically with other synergy hubs more than expected by chance. On the other hand, interaction between dissimilar hubs could either be redundant or synergistic. Homogenous subpopulations comprising synergy hubs are significantly better at decoding stimulus information compared to redundancy hubs or heterogeneous subpopulations comprising both synergy and redundancy hubs. Mechanistically, we find that synergistic interactions emerge from the stimulus dependence of correlated activity between groups of neurons. Our findings suggest a refinement of the prevailing ideas regarding coding schemes in sensory cortex: Columnar neuronal populations can efficiently encode information due to synergistic inter-neuronal interactions even when receptive fields overlap and shared noise between cells is high.

Disclosures: S. Nigam: None. **S. Pojoga:** None. **V. Dragoi:** None.

Nanosymposium

192. Information Seeking From Flies to Human

Location: Room N426

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 192.01

Topic: F.01. Neuroethology

Support: Leon Levy Foundation
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NIMH R01MH109690
NSF IOS1555933
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Klingenstein-Simons Foundation

Title: Neural circuits underlying active sensing in the *drosophila* antennal mechanosensory and motor system

Authors: *M. P. SUVER, K. I. NAGEL;
Neurosci. Inst., NYU Med. Ctr., New York, NY

Abstract: All animals move their sensors to obtain information about the world. However, few model systems permit genetic access to all of the sensory and motor circuits involved in distinguishing self- versus externally-generated sensations. Fruit flies, like most insects, can actively position their antennae, but how they use such movements to gain information about the sensory world is unclear. In a previous study (Suver et al. 2019), we identified a mechanosensory circuit in *Drosophila* that computes wind direction from movements of the two antennae. We showed that 2nd order AMMC projection neurons (APNs) encode ipsilateral antennal displacements, while 3rd order wedge projection neurons (WPNs) linearly encode wind direction in azimuth by combining input from both antennae. In ongoing work, we have begun to ask how neurons in this circuit encode externally- versus internally-generated (active) movements. Our preliminary results suggest differential encoding by 2nd and 3rd order neurons. We have also begun mapping the motor circuitry that controls active movements of the antennae. Using optogenetics, we activated putative antennal motor neurons and measured the resulting antennal deflections using machine learning analysis of video data. This approach has enabled us to identify several genetic lines that drive antennal movements and can be used to test the role of active antennal movements in sensory coding and mechanosensory-guided behavior. Together our work aims to develop the *Drosophila* antennal-motor system as a tractable model for understanding the neural basis of active mechanosensation.

Disclosures: M.P. Suver: None. **K.I. Nagel:** None.

Nanosymposium

192. Information Seeking From Flies to Human

Location: Room N426

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 192.02

Topic: F.01. Neuroethology

Support: Howard Hughes Medical Institute

Helen Hay Whitney Foundation

Title: Unsupervised learning of odor sequences in olfactory cortex

Authors: *A. J. P. FINK, C. E. SCHOONOVER, R. AXEL;
Neurosci., Columbia Univ., New York, NY

Abstract: Animals continuously learn features of their sensory environment in the absence of reinforcement. However, the neuronal mechanisms by which exploration and information seeking lead to a model of the external world are poorly understood. We have developed a behavioral paradigm for the head-fixed mouse that permits simultaneous observation of unsupervised learning and electrophysiological recording of large a population of single units in piriform cortex (PCx). Exposure to a sequence of two neutral odorants A->B initially elicits a strong behavioral response that habituates upon continual exposure over three days. After habituation to the A->B sequence, presentation of either A or B alone nonetheless elicits a strong behavioral response. Recordings in PCx demonstrate that continual exposure to the A->B sequence results in dramatic reduction in the magnitude of population responses, with a time course that matches long-term behavioral habituation. In naïve animals, population firing rates to the A and B sequence elements are comparable, but after continual exposure responses to A are lessened whereas responses to B are nearly abolished. However, a B stimulus presented alone elicits a strong response. Moreover, if A is presented but B omitted, PCx responds vigorously to the absence of B, producing a representation that matches the expected timing of the omitted stimulus but not the ensemble of neurons elicited by presentation of B. Taken together these concordant behavioral and electrophysiological results show that response magnitude of an odor representation in PCx inversely reflects the degree to which an event is expected. Learning therefore filters familiar events whereas unanticipated events are robustly represented. This suggests that PCx representations do not strictly reflect physical stimuli, but rather a model of the statistics of the olfactory environment, formed over the course of unsupervised learning.

Disclosures: **A.J.P. Fink:** None. **C.E. Schoonover:** None. **R. Axel:** None.

Nanosymposium

192. Information Seeking From Flies to Human

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Topic: F.01. Neuroethology

Support: Howard Hughes Medical Institute
Simons Foundation Society of Fellows Junior Fellowship
NIMH grant R01MH116937

Title: Information seeking in mice: A behavioral paradigm and imaging studies of neural circuits for the desire to know

Authors: *J. J. BUSSELL[1,2], E. S. BROMBERG-MARTIN[4], R. AXEL[1,2,3];
[1]Mortimer B. Zuckerman Mind Brain Behavior Inst., [2]Neurosci., [3]Howard Hughes Med. Inst., Columbia Univ., New York, NY; [4]Neurosci., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Animals are motivated to acquire knowledge. A particularly striking example is information seeking behavior: animals often seek out sensory cues that will inform them about the properties of uncertain future rewards, even when there is no way for them to use this information to influence the reward outcome, and even when this information comes at a considerable cost. Evidence from monkey electrophysiology and human fMRI studies suggests that orbitofrontal cortex and midbrain dopamine neurons represent the subjective value of knowledge during information seeking behavior. However, it remains unclear how the brain assigns value to information and how it integrates this with other incentives to drive behavior. We have therefore developed a task to test if information preferences are present in mice and study how informational value is imparted on stimuli. Mice are trained to enter a center port and receive an initial odor that instructs them to either go to an *informative* side port, go to an *uninformative* side port, or choose freely between them. The chosen side port then yields a second odor cue followed by a delayed probabilistic water reward. The informative port's odor cue indicates whether the upcoming reward will be big or small. The uninformative port's odor cue is uncorrelated with the trial outcome. Crucially, the two ports only differ in their odor cues, not in their water value since both offer identical probabilities of big and small rewards. We find that mice prefer the informative port. This preference is evident as a higher percentage choice of the informative port when given a free choice (67% +/- 1.7%, $n = 14$, $p < 0.03$), as well as by faster reaction times when instructed to go to the informative port (544ms +/- 21ms vs 795ms +/- 21ms, $n = 14$, $p < 0.001$). The preference for information is robust to within-animal reversals of informative and uninformative port locations, and, moreover, mice are willing to pay for information by choosing the informative port even if its reward amount is reduced to be substantially lower than the uninformative port. These behavioral observations suggest that odor stimuli are imparted with informational value as mice learn the information seeking task. We are currently imaging neural activity in orbitofrontal cortex with microendoscopes to identify changes in neural activity that may reflect value associated with the acquisition of knowledge.

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Nanosymposium

192. Information Seeking From Flies to Human

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Presentation Number: 192.04

Topic: F.01. Neuroethology

Support: NIMH Grant MH110594

Title: A neural network for information seeking

Authors: *E. S. BROMBERG-MARTIN[1], J. K. WHITE[1], S. R. HEILBRONNER[2], K. ZHANG[3], J. PAI[4,1], S. N. HABER[5], I. E. MONOSOV[1,3];
[1]Neurosci., Washington Univ. Sch. of Med., Saint Louis, MO; [2]Neurosci., Univ. of Minnesota, New Brighton, MN; [3]Biomed. Engin., Washington Univ., Saint Louis, MO; [4]Ctr. for Neural Sci., New York Univ., Brooklyn, NY; [5]Univ. of Rochester, Rochester, NY

Abstract: When faced with delayed and uncertain rewards, both humans and animals search for information from their environment to learn what their future holds. However, the neural systems that motivate information seeking have been primarily investigated in economic choice tasks. Less is known about the most fundamental form of natural information seeking behavior: shifting the eyes to inspect the source of uncertainty. We hypothesized that information seeking is motivated by a network of uncertainty-related neurons that we recently discovered in anatomically connected regions of the anterior cingulate cortex (ACC), dorsal striatum (DS), and ventral pallidum (VP). We tested this by training monkeys in an "information anticipation task" in which different visual conditioned stimuli (CSs) lead to different probabilities of juice reward, including some CSs predicting certain outcomes (e.g. 100% reward) and others predicting uncertain outcomes (e.g. 50% reward). Crucially, one set of *information-predictive* CSs are followed by *informative* visual cues that perfectly predict the trial's upcoming reward outcome (and hence resolve any uncertainty). A matched set of *non-information-predictive* CSs are followed by non-informative visual cues that do not predict the reward outcome. We found that a substantial population of neurons in all three areas of the network have strong and selective *information-anticipatory* activity: ramping activity that anticipates the moment when the animal expects to gain information about uncertain rewards. Furthermore, these signals are ideally suited to motivate information seeking behavior: (1) in parallel with these neural signals, animals make information-anticipatory eye movements to gaze at uncertain CSs and cues, (2) neural information signals have strong moment-to-moment correlations with gaze, such that fluctuations in neural signals predict future gaze shifts hundreds of milliseconds in advance, (3) pharmacological perturbation of the basal ganglia nuclei that contain these information signals causally interferes with information seeking gaze shifts. Thus, our data indicate that the ACC-DS-VP network has a crucial role in motivating behavior to resolve uncertainty by seeking information about the future.

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Nanosymposium

192. Information Seeking From Flies to Human

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Topic: F.01. Neuroethology

Support: NIH Grant 1K99DA048748-01

Title: Primates seek information to learn states of complex environments

Authors: *D. L. BARACK, C. D. SALZMAN;
Neurosci., Columbia Univ., New York, NY

Abstract: Whether negotiating social spaces, solving puzzles, or planning research, humans reason and learn in complex environments with many actions and states. From learning social hierarchies to planning a foraging route, nonhuman primates face similar problem spaces with many actions and states. Here, we report on monkeys and humans playing a simplified version of the game Battleship, designed to investigate learning these complex environments. Primates visually uncovered one shape per trial over multiple choices. Each shape occurred at a specific location, but shapes could overlap. Choices could be made in any order and revealed either a piece of the colored target or a white background. Trials ended once the shape was fully uncovered. Both humans and primates were adept at this task. We focus on two questions: what were primates learning during this task (e.g., shapes or movement sequences)?; and what computations were primates using to learn? Both monkeys and humans used different patterns to reveal the shape across learning, indicating that the shapes, and not movement sequences, were learned. This variability in movement patterns used to reveal shapes persisted well after shapes were learned. In addition, both monkeys and humans used a search strategy that maximized the reduction in uncertainty about the underlying shape in selecting squares during the task. This best-fit strategy maximized the expected reduction in entropy about environmental states assuming stochasticity in the evidence about the state. This model outperformed a range of reinforcement learning algorithms as well as models that lacked the assumption of stochasticity. We plan on recording from the orbitofrontal cortex to investigate the formation of task state representations of the underlying shapes during our task.

Disclosures: D.L. Barack: None. **C.D. Salzman:** None.

Nanosymposium

192. Information Seeking From Flies to Human

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Topic: F.01. Neuroethology

Support: Brain and Behavior Research Foundation
P&S Fund
Wharton Neuroscience Initiative

Title: How do stress and anxiety impact the neurobiology of foraging decisions?

Authors: *A. RAMAKRISHNAN, D. BERKAY, M. L. PLATT;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Efficiently foraging for information strongly shapes our ability to navigate the world. It has been hypothesized that information-seeking behavior is mediated by neural mechanisms that evolved to support foraging. The foraging behavior of animals, including humans, aligns with predictions made by optimality models, specifically the Marginal Value Theorem (MVT). Nevertheless, individuals vary considerably in their foraging strategies. Individual susceptibility to stress and anxiety may contribute to this variability in behavior. A neural circuit connecting posterior and anterior cingulate cortices (ACC) with the norepinephrenergic locus coerulus has been implicated in foraging decisions. And this network whose dysfunction may result in a negativity bias has also been implicated in anxiety and stress. We propose that understanding variation in foraging behavior and the impact of stress on the underlying mechanisms will help us to understand dysfunctional information-seeking biases in neuropsychiatric disorders like anxiety and depression and reveal new biomarkers for these disorders. To test this idea, in the first experiment we measured the behavior of human participants (N=45) performing a patch foraging task, while we monitored pupil size, reflective of norepinephrine tone, and EEG source-localized to the ACC. Individuals with high trait or state anxiety score abandoned patches earlier than predicted by the MVT. A supervised machine learning algorithm trained on time spent at a patch, pupil diameter and EEG, reliably predicted anxiety levels (high/medium/low) with ~70% accuracy. Next, to validate the effects of anxiety on foraging, in the second experiment we induced stress using a Trier Social Stress Test protocol and measured foraging behavior both before and after stress induction. As expected, we found that stress induced earlier patch-leaving decisions. Finally, we utilized a hierarchical drift diffusion model to understand the impact of stress on the decision making process. Overall, our results show that stress and anxiety impact foraging behavior. Behavioral variability along with the associated physiological manifestations could serve as biomarkers for early detection of anxiety and other neuropsychiatric disorders, particularly in individuals, such as children, for whom self-report is less reliable.

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Nanosymposium

192. Information Seeking From Flies to Human

Location: Room N426

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 192.07

Topic: F.01. Neuroethology

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Title: Deciding to sample: Modeling instrumental information demand and belief updating in humans

Authors: *N. M. SINGLETARY[1], J. P. GOTTLIEB[1,2], G. HORGA[3];
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Abstract: Prevalent approaches to modeling choice behavior and its neural correlates leave two major unanswered questions: how do decision makers (DM) estimate the value of additional information when making a choice, and how do they update their beliefs based on prior knowledge and new information? We investigate these questions using two variants of the Museum Task, a novel task, based on the Beads Task, that explores how human subjects demand instrumental information in the form of pictorial samples of faces and scenes, and how they use the information to update their beliefs. Subjects are given an endowment ($30), and they infer whether they are in a "portrait" gallery in which most pictures depict faces, or a "landscape" gallery in which most picture depict scenes, based on the prior probability of being in one type of gallery or the other (7-93%), the penalty for errors ($10 or $20), and the majority-to-minority ratio (57:43-93:7) of picture types in the gallery (an indicator of the likelihood probability). Pictorial samples allow for adaption to fMRI, where we can use the well-known face- and scene-selective brain regions. The task consists of two variants: the Willingness to Pay (WTP) Task and the Belief Updating (BU) Task. In the WTP task, subjects are told the prior probability, majority-to-minority ratio, and error penalty and bid for a sample picture to potentially improve their accuracy. In the BU task, subjects are told the prior probability, majority-to-minority ratio, and error penalty, along with a free sample picture, and estimate the posterior probability of being in one gallery or the other. We measured subjects' (n = 23) behavior as a linear function of the ideal observer models, based on Bayes' Rule, to solve the WTP and BU tasks. On the WTP task, consistent with the ideal observer's predictions, subjects' bids reflect a positive interaction between the error penalty and the expected information gain of the sample although they overbid compared to the ideal observer. On the BU Task, subjects incorporate the prior and likelihood probabilities into their posterior probability estimates but underweight both the prior and the likelihood relative to Bayes' Rule. The results show how people partially conform to, but also deviate from, Bayesian predictions and lay the groundwork for our current fMRI investigation of brain networks that underlie information sampling and probabilistic belief updating.

Disclosures: N.M. Singletary: None. **J.P. Gottlieb:** None. **G. Horga:** None.

Nanosymposium

192. Information Seeking From Flies to Human

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Presentation Number: 192.08

Topic: F.01. Neuroethology

Title: Modeling the dynamics of suspense

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Abstract: Suspense refers to the affective state that accompanies anticipation about the delivery of information. To explore the factors that induce suspense in humans, we designed a novel task similar to the card game Blackjack during which we asked people to subjectively rate their moment-by-moment feeling of suspense. Using a theory of suspense first proposed by Ely et al (2015), we designed stimuli to optimally induce a variety of suspense dynamics. We recruited 263 people (113 female), aged 36.7±20.4(mean±SD) from Amazon Mechanical Turk to perform the task. Each participant played two games designed according to the theory to be "low-suspense" and three games designed to be "high-suspense". A paired t-test showed that "low-suspense" games induced lower suspense ratings on average than "high-suspense" games, $t(262) = 14.2$, $p<.001$, confirming our basic manipulation check. The model also allowed us to present participants with identical sequences of information (i.e., card draws) while varying the context (i.e., the rules of the game) to manipulate suspense. We computed the average z-scored responses for each point in each high-suspense game and calculated the difference between two rules. The correlation coefficient between the reported suspense differences and model is 0.80 ($p=0.01$), with 78% of the suspense differences in the same direction as predicted. The model has no free parameters, making its correlation with participants' subjective and inherently noisy self-reported suspense impressive. Last, we compared a number of alternative models including heuristic models that equate suspense with current uncertainty or measures of peril (i.e., nearness to losing). Moreover, under the interpretation that suspense is an "expectation of future surprise", Ely et al. assumed an L2-norm (squared distance) to quantify "surprise" while we explored a range of alternatives including the L1-norm, information gain, KL-divergence and Hellinger distance. Ultimately, the L1-norm model provided the closest fit to the behavioral data. Overall, our results show the first empirical evidence linking the affective state of suspense to the metacognition about future belief change, or roughly "expected surprise". Our results also give support to the idea that suspense can also be interpreted as a self-evaluation of learning progress which is a central notion in research on information sampling and curiosity.

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Nanosymposium

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Topic: F.01. Neuroethology

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Title: Neural computations related to uncertainty-driven exploration in the human brain: A human single neuron study

Authors: *T. AQUINO[1], J. COCKBURN[2], A. MAMELAK[3], U. RUTISHAUSER[3,1], J. P. O'DOHERTY[2];
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Abstract: The neural mechanisms balancing the trade-off between exploration and exploitation are relatively unknown. One exploration strategy in reinforcement-learning is determining the uncertainty of the reward distribution available on an action (i.e. estimation uncertainty) and assigning a utility to that uncertainty to drive exploration. We previously demonstrated the presence of exploration-related variables such as expected values and the utility of estimation uncertainty using fMRI, in multiple brain regions, including vmPFC and amygdala. Here we aimed to address how exploration-related variables found in the fMRI BOLD signal are encoded at the single neuron level. For this, we recorded single neuron activity from intracranial microelectrodes from 7 epilepsy patients, while they performed the same bandit task as in our previous fMRI study, in which we manipulated expected value and estimation uncertainty, while controlling for stimulus novelty and the horizon of opportunity.
Using a reinforcement-learning model fit to patients' behavior, we tested for neuronal activity correlating with exploration-related variables. A Gaussian GLM analysis over 233 neurons revealed a significant number of amygdala and vmPFC neurons whose firing rate is modulated by expected reward during decision, consistent with the fMRI findings. We also found widespread neural sensitivity to the value of uncertainty of the chosen bandit, in amygdala, preSMA and vmPFC. Finally, at the time of outcome, we found a significant number of neurons sensitive to outcomes in vmPFC, hippocampus and amygdala; to reward prediction errors in amygdala; and to uncertainty in amygdala, preSMA and vmPFC, similarly to the decision period. These findings shed light on the role of different brain structures, notably amygdala and vmPFC in resolving the exploration-exploitation dilemma in the human brain. These structures contain representations not only of expected value for an option, but also a value signal for estimation uncertainty that can be used to drive exploration of unknown options. Our findings also highlight the importance of relating different measures of neural activity in humans in order to obtain a more complete understanding of how cognitive processes map to their underlying neural mechanisms.

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Nanosymposium

193. Functional Role of Sleep

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Topic: F.08. Biological Rhythms and Sleep

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Title: A key role for locus-coeruleus norepinephrine activity in mediating sensory-evoked awakenings from sleep

Authors: *H. HAYAT[1], N. REGEV[1], N. MATOSEVICH[1], A. SALES[2], E. PAREDES-RODRIGUEZ[2,3,4], A. J. KROM[1,5], L. BERGMAN[1], Y. LI[2], M. LAVIGNE[6], E. J. KREMER[6], O. YIZHAR[7], A. E. PICKERING[2,8], Y. NIR[1,9];
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Abstract: A defining feature of sleep is reduced responsiveness to external stimuli, but the mechanisms gating sensory-evoked arousal remain unclear. We hypothesized that reduced locus-coeruleus norepinephrine (LC-NE) activity during sleep mediates unresponsiveness, and its action promotes sensory-evoked awakenings. We tested this using electrophysiological, behavioral, pharmacological, and optogenetic techniques alongside auditory stimulation in freely behaving rats. We found that systemic reduction of NE signaling (detomidine, 1mg/kg) lowered probability of sound-evoked awakenings (SEAs) (n=6 rats). Chronic recordings of LC spiking activity revealed that the level of tonic LC activity during NREM sleep anticipated SEAs (n=9 units). The LC was transduced with CAV-PRS-ChR2-mCherry to allow selective optogenetic stimulation which promoted arousal as evident in sleep-wake transitions, EEG desynchronization, and pupil dilation. Importantly, liminal LC excitation before sound presentation increased SEA probability from both NREM and REM sleep (n=8 rats).

Optogenetic LC silencing using a soma-targeted anion-conducting channelrhodopsin (CAV-PRS-stGtACR2-FRed) suppressed LC spiking and constricted pupils. Brief periods of LC opto-silencing reduced the probability of SEAs from NREM sleep (n=6 rats). Thus, LC-NE activity determines the likelihood of sensory-evoked awakenings and its reduction during sleep constitutes a key factor mediating behavioral unresponsiveness.

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Nanosymposium

193. Functional Role of Sleep

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Presentation Number: 193.02

Topic: F.08. Biological Rhythms and Sleep

Title: Electrophysiological and non-electrophysiological markers of fulfillment of sleep homeostatic need

Authors: *B. R. SHETH, A. SURELIA;
Univ. of Houston, Houston, TX

Abstract: Sleep is a critical homeostatic need across the animal kingdom. Slow-wave activity (SWA: spectral power in 1-4 Hz frequency range of the electroencephalogram, or EEG), and time spent in the deepest sleep stage, i.e. slow-wave sleep (SWS), are directly related to time spent awake and, therefore, likely to fulfill sleep need. Several questions remain. **1**) For a given individual, is sleep need met by increased SWA, increased SWS duration, either but not both, or both? **2**) SWA is found in all sleep stages, but is highest in SWS; achieving sleep homeostasis by increasing SWA in SWS is more efficient than increasing SWA in stage 2 (S2) of non-REM sleep. Is SWA in S2 related to SWS duration in a similar way as SWA in SWS? **3**) In parallel with SWA in S2 versus in SWS is time spent in SWS and in S2. Does increased SWS duration mean increased S2 duration? In order to address these questions, we analyzed EEG data from the Sleep Heart Health Study database – a multi-center cohort study implemented by NHLBI and consisting of a study of 5804 adults aged 39-90. Our between-subject analysis revealed the following: **1**) A strong, significant positive correlation between SWA in SWS and SWS duration ($\rho = 0.652$, $p = 0$); within-subject analysis from subjects (Ss) with two nights of recordings was in agreement with the above between-subject analyses, revealing a significant proportion (1404/2329 Ss = 60%) of lines with positive slope ($p = 1.40 * 10^{-23}$, binomial test). **2**) A strong, significant positive correlation between SWA in S2 and SWA in SWS ($\rho = 0.826$, $p = 0$) and between SWA in S1 and SWA in SWS ($\rho = 0.455$, $p = 5.453* 10^{-263}$); within-subject analysis also showed a significant proportion (1813/2347 Ss = 77%) of lines with positive slope (p =

3.46* 10^{-162}). **3**) A strong, significant *negative* correlation between SWA in S2 and S2 duration (ρ = -0.370, p = 2.29* 10^{-167}) and between SWA in S2 and S1 duration (ρ = -0.352, p = 4.26* 10^{-151}); within-subject analysis also showed a significant proportion (1371/2330 Ss = 59%) of lines with positive slope (p = 6.91* 10^{-18}).
Our findings of strong positive relationships among the triad of SWS duration, SWA in SWS, and SWA in S2 (and in S1), and strong negative relationships of said triad with S2 duration (and S1 duration) argue for the following: SWA is *the* key to sleep homeostasis; given that SWA content is highest in SWS, it is efficient for the organism to be in SWS; however, the brain cannot change state directly from wake to SWS, but rather must transition through sleep stages S1 and S2 as quickly as possible prior to reaching SWS.
Current research is focused on establishing a relationship between markers of sleep need in wake and the triad of markers associated with the fulfillment of sleep need.

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Nanosymposium

193. Functional Role of Sleep

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Topic: F.08. Biological Rhythms and Sleep

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Title: FoxP2 cells in the lateral parabrachial area regulate respiratory response to hypercapnia

Authors: *S. KAUR, C. B. SAPER;
Beth Israel Deaconess Med. Ctr. and Harvard M, Boson, MA

Abstract: We have previously reported that CGRP neurons in the external lateral parabrachial nucleus (PB^{CGRP}) play a critical role in transmitting the arousal signal to cause EEG desynchronization in response to hypercapnia. A second population of neurons adjacent to the PB^{CGRP} group, which projects to respiratory control areas in the medulla, are marked by expression of the transcription factor FoxP2. We hypothesize that while the PB^{CGRP} neurons wake up the forebrain during apneas, the adjacent PB^{FoxP2} neurons may trigger sudden activation of the airway dilators and other components of the respiratory system during apnea.
We first exposed mice (n=3) to 2h of 10% CO2, and tested if PB^{FoxP2} cells can be activated by such exposure, by double- immunostaining the brain tissue for both FoxP2 and cFos. We found that PB^{FoxP2} neurons showed cFos activation during CO2 exposure, but that none of them also stained for CGRP.
Second, we investigated the response of either optogenetic inhibition or activation of PB^{FoxP2}

neurons on respiration. We injected FoxP2Cre mice bilaterally in the PB with adeno-associated virus containing the gene for either channel rhodopsin2 (AAV-FLEX-ChR2-mCherry; n=2, for neuronal activation) or archaerhodopsin T TP009 (AAV-FLEX-ArchT-GFP ArchT; n=2, for neuronal inhibition) in a Cre-inducible FLEX cassette that expressed either ChR2 or ArchT only in the PB^{FoxP2} cells. These mice were prepared for sleep recordings and were implanted with bilateral optic fiber targeting the PB.
Blue laser (473nm) light targeted to the PB, activated ChR2 expressing neurons with 10ms pulses of 473nm given at 5, 10 and 20Hz, for 5s every 5 minutes, without any hypercapnia stimulus and then respiration was measured. Photo-stimulation of ChR2 expressing PB^{FoxP2} at 10Hz for 5s increased the respiratory rate (RR) by 25% and Tidal volume (V_T) by 45%, with no effect at 5 Hz. At 20 Hz for 5s, RR increased by 63% and V_T by 62%. Animals aroused in most trials towards the end of the 5s stimulation period.
We also investigated the respiratory response to10% CO2 given for 30s every 300s, with and without photo-inhibition of the PB^{FoxP2} neurons with 593 nm laser light. Laser light was on for 60s beginning 20s prior and extending 10s after the CO2 stimulus. Inhibition of the PB^{FoxP2} cells caused reduction in RR, V_T, and minute ventilation (MV) during the time the animals were exposed to CO2 both before and after EEG arousal, without affecting the latency of arousal from CO2.
Preliminary GCaMP fiber photometry recordings suggested that the firing of the PB^{FoxP2} neurons roughly parallels the increasing ventilation, thus corroborating the role of PB^{FoxP2} neurons in regulating respiratory response to hypercapnia.

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Nanosymposium

193. Functional Role of Sleep

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Topic: F.08. Biological Rhythms and Sleep

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Title: A polymorphism of the proinflammatory cytokine TNFα gene is associated with resilience to performance impairment from sleep deprivation and the effectiveness of caffeine

Authors: L. SKEIKY[1], D. A. HANSEN[1], B. C. SATTERFIELD[2], M. PETROVICK[3], T. J. BALKIN[4], R. H. RATCLIFFE[4], V. F. CAPALDI[4], H. P. A. VAN DONGEN[1], ***A. J. BRAGER**[4];
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Systems and Technologies, MIT Lincoln Labs., Cambridge, MA; [4]Behavioral Biol., Walter Reed Army Insitute of Res., Silver Spring, MD

Abstract: Introduction: Sleep homeostasis is tightly connected with the immune system. TNFα, a proinflammatory cytokine, plays a key role in physiological sleep regulation and various aspects of cognition. Carriers of the A allele of a single nucleotide polymorphism of the TNFα gene (G308A, rs1800629) have been found to be resilient to cognitive impairment due to total sleep deprivation (TSD) as compared to individuals homozygous for the G allele. Caffeine mitigates the cognitive impairment associated with sleep deprivation. Here we investigate whether TNFα genotype affects the impact of caffeine on cognitive impairment during sleep deprivation. **Methods:** In an 18-day controlled in-laboratory study, 12 healthy adults (age 27.4 ± 6.9; 6 females) underwent three sessions of 48-hour TSD, with each TSD session preceded and followed by three nights of baseline and/or recovery sleep (10 hours time in bed each). In randomized, counterbalanced, double-blind, placebo-controlled fashion, during each TSD session a specific dose of caffeine (0, 200, or 300 mg) was administered four times at 12-hour intervals. Vigilant attention performance was measured every 2 hours during each TSD session by means of a psychomotor vigilance test (PVT), for which the log of the signal-to-noise ratio (LSNR) was determined as a measure of the fidelity of information processing. Each subject's TNFα genotype was assessed from a whole blood sample. **Results and Discussion:** Subjects homozygous for the TNFα G allele showed greater PVT impairment during sleep deprivation in the 0 mg caffeine (i.e., placebo) condition as compared to carriers of the A allele and as compared to the 200 and 300 mg caffeine conditions (mixed-effects ANOVA, TNFα genotype by caffeine dose interaction: $F_{2,566}$=5.23, unadjusted P=0.005). There was no appreciable caffeine-related difference in performance for carriers of the A allele, who were relatively resilient to TSD regardless of caffeine dose. These data show that genetic variants of the immune system may mediate individual differences in performance under TSD and indicate non-additive effects of TNFα genotype and caffeine.

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Title: Sleep deprivation reverses the contributions of reticular formation and sympathetic tone to cortical activity

Authors: *E. SHOKRI-KOJORI[1], S. B. DEMIRAL[1], D. TOMASI[1], G.-J. WANG[1], N. D. VOLKOW[2];
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Abstract: While sleep deprivation (SD) results in complex changes in neurotransmitter activity and autonomic function, it is not fully understood how these changes could modify brain activity. Previously we have shown that SD results in significant increases in fMRI-based measures of brain activity within an autonomic network (AN). This network included the dorsal attention stream and visual and sensorimotor cortices, which together exhibited significant interactions with vascular sympathetic tone as indexed by low frequency (LF, < 0.1 Hz) fluctuations in the pulse signal. Here we explored whether brain regions, particularly those related to arousal signaling, alter their temporal synchrony with sympathetic tone during SD, and to what extent these changes are related to increases in activity within the AN. In a group of 20 healthy individuals (10 females, 22-72 years old), we measured brain resting-state activity with fMRI (10 min) and concurrently recorded the pulse signal, once after rested wakefulness (RW) and once after one night of total SD. Whole-brain analysis of LF phase (indexing temporal lag) between pulse and brain signals in SD versus RW, revealed significant changes in the LF phase ($p_{FWE} < 0.05$) in a medial network (MN) including midbrain and thalamus, superior and medial frontal gyri, anterior and posterior cingulate and precuneus. The strongest effect in MN was present bilaterally within the midbrain reticular formation. On average, the LF phase changed from 0.04 rad to -0.37 rad from RW to SD ($p < 0.001$), indicating that activity in MN preceded sympathetic tone in SD (but not in RW). Interestingly, LF fluctuations in the AN were positivity associated with the LF phase between MN and pulse signals in RW ($r(18) = 0.56$, $p = 0.01$), while LF fluctuations in the AN were negatively associated with the LF phase between MN and pulse signals in SD, across participants ($r(18) = -0.65$, $p = 0.002$). Despite minimal spatial overlap between AN and MN, our results highlight that SD reversed the association between AN activity and MN-sympathetic interactions ($z = 4.11$, $p < 0.001$). These findings shed further light on the importance of studying the relative timing of brain activity and autonomic signaling and how physiological conditions such as SD could alter this timing and its association with cortical activity. Future characterization of the observed effects should investigate the potential role of acetylcholine and norepinephrine neurotransmitter systems that are critical for the function of midbrain reticular formation and sympathetic nervous system.

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Topic: F.08. Biological Rhythms and Sleep

Title: Proboscis extensions during sleep: A new sleep stage in *drosophila* with a functional role in waste clearance

Authors: *B. VAN ALPHEN[1], E. R. SEMENZA[1], M. YAP[2], B. VAN SWINDEREN[2], R. ALLADA[1];
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Abstract: Sleep is our most vulnerable state, as we are unaware of predators and other dangers in our environment for long stretches of time. Nevertheless, sleep is widely conserved throughout the animal kingdom, suggesting it fulfills functions important enough to offset these risks. Although the exact function of sleep remains unknown, its proposed functions include memory consolidation and metabolite clearance. In mammals, metabolite clearance is thought to be achieved through the glymphatic system. Sleep in invertebrates has all the hallmarks of mammalian sleep, including homeostasis, altered brain activity, stages of lighter and deeper sleep and a characteristic posture. Whether sleep facilitates waste clearance through a glymphatic system or otherwise remains unclear.
We discovered a discrete sleep stage in *Drosophila*, during which the fly repeatedly and spontaneously extends and retracts its proboscis in a stereotypical manner during inactivity and without any apparent external stimulus, e.g, food exposure. Experiments in tethered flies showed that, during these proboscis extensions (PE), arousal thresholds are increased and brain activity is decreased, indicating a deep sleep stage. PE increases after sleep deprivation, suggesting there is a homeostatic mechanism underlying this behavior. PE occur more frequently after injury and preventing PE increases mortality after injury, suggesting that PE are part of a recovery mechanism, potentially through facilitating clearance.
Drosophila only has a rudimentary circulatory system. Organs are bathed in hemolymph, which delivers nutrients and collects waste. Waste is filtered from the hemolymph by Malphigian tubules that deliver it to the gut, from where it is excreted. To test whether PE facilitate waste clearance, we injected dye into the fly hemolymph and measured the rate at which dye is excreted. Preventing proboscis extensions slows down the rate at which dye is excreted. Together, these results provide a first glimpse at how invertebrate sleep facilitates waste clearance. During sleep, *Drosophila* intermittently uses its proboscis as a pump to increase the rate at which hemolymph flows through its body, increasing waste clearance rate.

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Title: Impact of chronically fragmented sleep on cortical electroencephalogram power spectra in rats

Authors: *K. A. MAKI, A. NAKVOSAITE, B. ICZI BALSERAK, M. W. CALIK, A. M. FINK;
Univ. of Illinois at Chicago, Chicago, IL

Abstract: Power spectral analysis of the cortical electroencephalogram (EEG) is a useful tool for examining the effects of chronic sleep fragmentation (SF) on brain activity. Low-frequency oscillations correlate with the depth of sleep. To test the hypothesis that SF causes prolonged alterations in EEG parameters during sleep and wake states, we conducted polysomnography (PSG) recordings in Wistar-Kyoto rats. We examined spectral EEG bands (delta, 0-4 Hz; theta, 4-8 Hz; alpha, 8-12 Hz; and beta, 16-24 Hz) before, during, and after SF. Male rats (n = 10) were implanted with telemetry transmitters to measure cortical EEG and nuchal muscle electromyogram (Data Sciences International [DSI]). Rats were acclimated to recording cages (SF chambers, Lafayette Neuroscience). The light/dark cycle was maintained with Zeitgeber Time (ZT) 0-12 representing light-phase, and ZT 12-24 representing dark-phase. All rats underwent 48-hr PSG to measure baseline EEG activity. Rats were randomized to SF (n=5) or undisturbed (n=5) for the following 28-days. SF was caused by turning on the SF chamber (ZT 1-9 daily) to activate a bar that swept the chamber bottom every 7 sec. Undisturbed rats slept *ad libitum* and served as a control group (C). During the last 48-hrs of SF, PSGs were repeated. EEG signals were scored in 10-sec epochs. EEG relative power was quantified using fast Fourier transformation over 10-sec intervals. A Hamming window was applied to each segment (NeuroScore, DSI). SF had a significant impact on delta and beta power. Compared with C, SF rats had a lower relative delta power (SF: 24.9±5.4% versus C: 18.8±5.1%, $p<0.01$) and higher relative beta power (SF: 8.9±1.1% versus C: 9.8±1.3%, $p<0.01$). Theta and alpha bands were not affected by SF. Light- vs. dark-phase comparison indicated no difference in the power spectra of SF rats despite the ability to rest during the dark-phase; SF rats had the same relative delta power during the light-phase, which included 16-hrs of SF (18.7±4.7%), and the dark phase (18.6±5.0%). In ongoing work, we are examining power spectra during recovery to determine the time required for EEG parameters to recover. Our findings suggest that EEG spectra during sleep and wake states are altered by SF, and detrimental effects are sustained during rest periods. Our model has implications for determining optimal rest periods required for replenishing the effects of chronically poor sleep. The methods may be useful for testing hypotheses about the effects of chronic illnesses or prolonged work schedules in humans.

Disclosures: **K.A. Maki:** None. **A. Nakvosaite:** None. **B. Iczi Balserak:** None. **M.W. Calik:** None. **A.M. Fink:** None.

Nanosymposium

193. Functional Role of Sleep

Location: Room S404

Time: Sunday, October 20, 2019, 1:00 PM - 4:15 PM

Presentation Number: 193.08

Topic: F.08. Biological Rhythms and Sleep

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Medical Research Council New Investigator Research Grant MR/L003635/1

Title: The interaction between subcortical sleep-wake circuitry and sleep homeostasis

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Abstract: The occurrence of wakefulness and sleep is controlled by several subcortical neuromodulatory structures, including the preoptic region of the hypothalamus, which are thought to trigger rapid transitions between vigilance states. In addition, the amount, timing and intensity of sleep are determined by preceding sleep-wake history. It remains unknown how and at what level these two systems of sleep regulation interact. To address this question, we performed continuous recordings of sleep and waking in freely moving adult male C57BL/6J mice (n=10), expressing ChR2 in GAD2 neurons, which underwent repetitive photostimulation (2-min trains at 10 Hz every 20 min) by blue light delivered via an optic fiber targeted above the preoptic area of the hypothalamus. In a subset of animals, stimulation was also performed over a 4-h period either following undisturbed sleep or after a 4-h sleep deprivation (SD).
First, we observed that stimulation reliably triggered an awakening in all animals, which occurred on average 14.9±1.8 and 22.7±2.9 seconds after the onset of stimulation during NREM sleep and REM sleep respectively ($p<0.05$), and the animals returned to sleep on average 5.2±0.4 and 5.0±1.0 min upon cessation of stimulation. As expected, stimulation did not produce an awakening in control animals (n=8). While every series of light flashes woke the animals up, the overall daily amount of sleep was not different between baseline and the day with stimulation (12.0±0.4 vs 11.6±0.5 hours respectively, n.s.). Furthermore, the total amount of EEG slow wave energy (SWE, cumulative spectral power between 0.5-4Hz in NREM sleep) attained during 24 hours was nearly identical between the experimental days. These results indicated that sleep loss produced by photoactivation of GAD2-expressing neurons in the hypothalamus triggered an adequate homeostatic response.

Finally, we compared the efficacy of stimulation during the 4-h interval after undisturbed sleep and after SD. In both cases stimulation produced an arousal, which occurred 14.0±1.1 and 13.6±1.8 seconds after the onset of stimulation respectively (n.s.). However, the latency to fall asleep upon cessation of stimulation was significantly shorter after SD than in the undisturbed sleep condition (4.8±0.6 vs 3.5±0.5 min, $p<0.05$). This suggests that activity modulation of sleep/wake promoting circuitry, while triggering state change, did not obliterate the "memory" of preceding sleep-wake history.
Altogether, our preliminary results suggest that the circuitry responsible for sleep-wake switching, at least in the preoptic hypothalamus, is likely to be independent of the system that underlies sleep homeostasis.

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Nanosymposium

193. Functional Role of Sleep

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Topic: F.08. Biological Rhythms and Sleep

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Clinical Research Priority Program (CRPP) Sleep and Health of the University of Zurich
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Title: Electroencephalography slow wave slopes as a marker for synaptic down-selection during sleep across development

Authors: *V. JARAMILLO[1,2], C. VOLK[1,2], M. FURRER[1,2], S. FATTINGER[1,2], S. KURTH[3], C. LUSTENBERGER[4], R. HUBER[1,2,5];
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Abstract: After a day of waking, a good night of sleep restores efficient brain functioning. This restorative function of sleep was proposed to be associated with a net reduction in synaptic strength. Recently, it has been proposed that the reduction of synaptic strength occurs in a "smart", comprehensive manner: while most synapses are selected for renormalization during sleep, a fraction of synapses is protected from down-selection. Major synaptic restructuring takes

place during brain development and impairments in synaptic down-selection during sleep may lead to cognitive and memory deficits in clinical populations (e.g. epilepsy). Slow waves, a major characteristic of non-rapid eye movement (NREM) sleep, are thought to mediate this down-selection. While both the amplitude and the slope of slow waves decrease during sleep, the slope has been shown to most directly reflect synaptic strength, when accounting for amplitude changes across the night. In this study, we aimed to investigate overnight slope changes in the course of development in a region- and amplitude-dependent manner. All-night high-density EEG was recorded in 60 healthy subjects aged between 8 and 30 years (mean ± s.e.m., 18.9 ± 0.8 years, 25 females). To control for amplitude changes across the night, we matched slow waves from the first and the last hour of NREM sleep according to their amplitude. Our results show that slow wave slopes decreased from the first to the last hour of NREM sleep (F_{time} (1,58) = 289.6, $p < 0.001$, linear mixed model) across the cortex. This global overnight slope change was largest in children and decreased with age ($r = - 0.510$, $p < 0.001$, Pearson correlation). Topographical analyses revealed regional differences in the slow wave slope decrease which were dependent on amplitude. Specifically, for small amplitude waves the decrease was smallest over an occipital area, whereas for large amplitude waves, the decrease was smallest over a central area ($F_{occipital}$ (7,392) = 4.81, $p < 0.001$, $F_{central}$ (7,392) = 8.75, $p < 0.001$, linear mixed model). The larger slope decrease in children might be indicative of a boosted down-selection of synapses during sleep in childhood, which, in turn, might be related to increased plasticity during brain maturation. Regional differences in the extent of slow wave slope reduction may reflect the "smart" down-selection process or, alternatively, indicate amplitude dependent differences in the generation of slow waves. These results reveal the need to consider age when using the overnight slope change as biomarker in clinical populations.

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Nanosymposium

193. Functional Role of Sleep

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Presentation Number: 193.10

Topic: F.04. Stress and the Brain

Support: P50 AT008661-01

Title: Altered circadian regulation of inflammasome activity in response to chronic sleep deprivation: Implications for Alzheimer's disease

Authors: C. SMITH[1], *K. TRAGESER[1], F. HERMAN[1], G. M. PASINETTI[1,2];
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Abstract: Chronic sleep deprivation (CSD) is prevalent throughout society and increases susceptibility to a number of chronic disorders including Alzheimer's disease. Here, we investigate whether the dysregulation of circadian rhythmicity by CSD leads to improper inflammatory activity involving the NLRP3 inflammasome. This multiprotein complex generates neuroactive cytokines in response to cellular stress and may link sleep deprivation with increased inflammation. We show that immediately following CSD there is altered hippocampal expression of *bmal1* ($p < .05$) and *clock* ($p < .05$) at ZT12. Following CSD, mice show increased expression of inflammatory genes including *nlrp3* ($p < .001$), *pro-IL-1b* and high mobility group box protein 1- (*hmgb1)* ($p < .05$), as well as extensive microgliosis ($p < .001$). Mice exposed to CSD also show upregulation of pro-inflammatory cytokines including IL-6 ($p < .05$) and IL-10 ($p < .05$). These mice also exhibited altered behavioral phenotypes as assessed by an open field paradigm, demonstrating increased anxiety ($p < .05$). Mice that are BMAL1-deficient similarly exhibited increased expression of *nlrp3* ($p < .05$) and extensive microgliosis ($p < .001$). Our data supports that loss of circadian rhythmicity increases susceptibility for neuroinflammation and altered behavioral phenotypes. Further supporting a direct contribution of NLRP3 to pathophysiologies associated with loss of circadian rhythmicity, NLRP3 deficient mice exhibited resilience to anxiety in response to CSD ($p >.05$) and did not exhibit microgliosis ($p >.05$) or upregulation of *hmgb-1 ($p<0.05$)*, previously observed following CSD. These results highlight how dysregulation of immune function by altered circadian rhythmicity in response to CSD, increases susceptibility for pathophysiologies associated with Alzheimer's disease. Further investigations are exploring the precise transcriptional and epigenetic mechanisms in microglia that may link circadian and immune activity.

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Nanosymposium

193. Functional Role of Sleep

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Topic: F.08. Biological Rhythms and Sleep

Support: The University of California Institute for Mexico and the United States (UC MEXUS)
Consejo Nacional de Ciencia y Tecnología (CONACyT)
Escuela de Medicina, Universidad Anahuac Mayab

Title: The synthetic cannabinoid agonist win 55, 212-2 injected in young animals blocks the sleep rebound after total sleep deprivation in adulthood

Authors: *M. E. DE LA CRUZ DELGADO, A. VERA-BARRON, K. ROMERO-CORDERO, L. MACIAS-TRIANA, A. TATUM-KURI, G. ARANKOWSKY-SANDOVAL, D. PIOMELLI,

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Univ. Anahuac Mayab, Merida, Yucatan, Mexico

Abstract: More than 500 molecules have been identified as components of *Cannabis sativa*, of which the most studied is Δ^9-tetrahydrocannabinol (Δ^9-THC). Several studies have indicated that Δ^9-THC exerts diverse biological effects, ranging from fragmentation of DNA to behavioral disruptions. Currently, it is accepted that most of Δ^9-THC effects engage the activation of the cannabinoid receptors, named CB_1 and CB_2. Based in recent events, legal use of *Cannabis sativa* for medical or recreational purposes would significant further health issues to be addressed. For example, it has been reported the use of *Cannabis sativa* in young subjects for medical purposes in the USA, such as epilepsy. Moreover, the accelerating legal and social acceptance of medicinal cannabis-based products for managing epilepsy in children will increase the legal use of cannabinoids in young subjects for other health issues. Therefore, unknown neurobiological long-term effects derived from use of cannabinoids in young population would represent a putative public health risk. At this date, most of the reports regarding the pharmacological effects of cannabinoid agonist have been developed in animal models under chronic and short-term experimental designs with no evidence about long-term effects. Thus, here we report the effects of chronic treatment in adolescent rats with WIN 55, 212-2 on the sleep homeostasis mechanism in adulthood. From postnatal day 30, animals received during 2 weeks a daily injection of either VEH (control; 1mL, intraperitoneally [i.p.]), or WIN 55, 212-2 (0.1, 0.3 or 1.0 mg/Kg/1mL, i.p.). In adulthood (post-natal day 80), electrodes for sleep recordings (EEG/EMG) were implanted in all animals. Total sleep deprivation was carried out during 6h across the lights-on period. Once finishing the sleep deprivation period, animals were allowed to sleep ad libitum for the next 4h. We found that treatments with WIN 55, 212-2 during young ages of animals caused a blocking effect of sleep rebound. Sleep quantity of slow wave sleep (SWS) and rapid eye movement sleep (REMS) during the sleep rebound period was decreased in experimental groups. Our study suggests that chronic stimulation of the CB_1 cannabinoid receptor in young animals induces alterations in the sleep homeostatic mechanism after total sleep deprivation in adulthood.

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Nanosymposium

193. Functional Role of Sleep

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Topic: F.08. Biological Rhythms and Sleep

Support: The University of California Institute for Mexico and the United States (UC MEXUS) and Consejo Nacional de Ciencia y Tecnología (CONACyT; Grant: CN-17-19) and Escuela de Medicina, Universidad Anáhuac Mayab (Grant: PresInvEMR2017) given to E.M-R.

Title: Chronic injections of cannabidiol in young rats cause sleep disturbances in adulthood

Authors: *D. MORALES-LARA[1,2], F. RAMÍREZ-TOSCANO[1,2], M. RUZ-ALCOCER[1,2], L. VIVAS-SANDOVAL[1,2], G. ARANKOWSKY-SANDOVAL[3], E. MURILLO-RODRÍGUEZ[1,2]; [1]Lab. de Neurociencias Moleculares e Integrativas, Univ. Anáhuac Mayab, Escuela De Medicina, Mérida, Mexico; [2]Intercontinental Neurosci. Res. Group, Mérida, Yucatán., Mexico; [3]Ctr. de Investigaciones Regionales "Dr. Hideyo Noguchi" Univ. Autónoma de Yucatán, Mérida, Yucatán., Mexico

Abstract: Most of the effects of use of *Cannabis sativa* in health have been linked to the activity of specialized G-protein-coupled transmembrane proteins (CB_1 and CB_2 cannabinoid receptors), and endogenous (anandamide and 2-AG) or exogenous (Δ^9-tetrahydrocannabinol and CBD) cannabinoids. Despite that significant advances in the understanding of the effects of cannabinoids in human health have been achieved, further complexity has been identified since the accelerating acceptance of medicinal cannabis-derived products for managing epilepsy or autism in children. Thus, one may imagine, the use or abuse of cannabinoids in young population would represent a public health issue since unknown neurobiological long-term effects have not been described yet. Here, we investigated the effects of chronic treatment in adolescent rats with CBD on the sleep-wake cycle during adulthood. From postnatal day (PND) 30, animals received for 2 weeks a daily injection of either VEH (control; 1mL, intraperitoneally [i.p.]), or CBD (5 or 30 mg/Kg/1mL, i.p.). In adulthood (PND-80), electrodes for sleep recordings (EEG/EMG) were implanted in all animals and they were recorded during 7 continuous days. Our results showed that pharmacological treatments caused no statistical changes in total time of wakefulness (W), whereas slow wave sleep (SWS) was enhanced and rapid eye movement sleep (REMS) was decreased. Data from 12h lights-on period showed that adult animals displayed a significant increase in W whereas SWS and REMS were decreased. In opposite direction, during 12h of lights-off period a significant diminution in W was found as well as an enhancement in SWS with no changes in REMS. Our study suggest that chronic administrations of CBD in young animals provoke sleep disturbances in adulthood.

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Nanosymposium

193. Functional Role of Sleep

Location: Room S404

Time: Sunday, October 20, 2019, 1:00 PM - 4:15 PM

Presentation Number: 193.13

Topic: H.02. Human Cognition and Behavior

Support: European Commission

Title: Detecting cued memory replay during slow-wave sleep and rapid eye movement sleep using EEG classifiers

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Abstract: Targeted Memory Reactivation (TMR) was used during REM and SWS to determine how reactivation in these stages impacts consolidation. Participants spent an adaptation night in the lab then performed the serial reaction time task, learning two 12 item sequences of button presses cued by pictures and tones but differing in finger order and tones. Participants then heard/saw the cues, and imagined doing the task. Tones associated with one of the sequences were then re-presented during subsequent REM (n=15) or SWS (n=15) to trigger replay. Importantly, these tones had also been presented during the adaptation night as a control.
TMR facilitated overnight improvement in sequence skill ($p = 0.04$) when data was pooled across SWS and REM groups.
Following prior work with this task[1] we built a classifier to detect the triggered reactivation during sleep using EEG data. This was trained on left and right hand in the imagination condition during wake, using time-domain features. The classifier was then applied after each tone during sleep.
In SWS, but not REM, cluster based permutation showed two clusters that classified significantly higher for the experimental night compared to the control night (sample-specific test statistic threshold=0.05, permutation test threshold=0.025, and n=12). The first cluster occurred directly after cue onset and the second occured ~1 sec. later.
We used the 300 trials that classified most strongly based on their probability, and noticed that the two significant peaks did not necessarily happen in the same trials. Some trials have two peaks and others only one. Contrary to prior work[1] we were able to detect replay any time during the SWS stimulation period, suggesting that replay likelihood did not decrease after repeated stimulation. We searched for a relationship between overnight behavioural improvement and detected replay and found a negative relationship with detected replay, spearman correlation =-0.57, $p= 0.056$. Because sleep spindles are strongly associated with memory replay, we searched for a relationship between spindle power at 11-16 HZ and detected replay, and revealed that the first classification peak predicted spindle power at 1.25-1.75 sec post cue. (spearman correlation=0.69, $p=0.017$).
In summary, our classifier detected TMR cued memory replay of motor imagination, in SWS. These detections occurred throughout the stimulation period, predicted subsequent spindle power, and negatively predicted behavioural consolidation. Interestingly, the replay appears to occur more than once after a sound cue.

1.
Belal, S. *et al.* Identification of memory reactivation during sleep by EEG classification. *Neuroimage* **176,** (2018).

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Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

Location: Room S104

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 194.01

Topic: G.01. Appetitive and Aversive Learning

Title: Reward learning shapes the fear circuit

Authors: *M. J. SHARPE[1], H. M. BATCHELOR[2], L. E. MUELLER[2], G. SCHOENBAUM[2]; [1]UCLA, Los Angeles, CA; [2]Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD

Abstract: The Lateral Hypothalamus (LH) has been traditionally viewed as providing an innate drive to approach rewards as dictated by other “cognitive” structures, such as prefrontal cortex. However, we have now shown that the GABAergic population in LH encodes learnt associations between cues and rewards (Sharpe et al., 2017, *Current Biology*). This allows LH to contribute to more complex forms of behaviour without input from higher-order structures. Given this new research, we were interested to see whether the role for the LH in cognition would be seen when learning to encode fear memories. Accordingly, we optogenetically inactivated LH GABAergic neurons during fear learning. Interestingly, we found that these neurons were not involved in learning to associate cues with mild foot shocks in naïve rats. However, if these rats had previously learnt to associate cues and rewards, GABAergic neurons then became necessary for rats to learn about the predictors of fear. Control experiments showed that this dissociation could not be accounted for by generalisation between fear and reward learning in these procedures. Effectively, having prior experience with learning about rewards shaped the neural circuits that were involved in learning about fear. These data have important consequences for the treatment of trauma-related disorders as they suggest previous experience could change where the fear memory is encoded.

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Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

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Presentation Number: 194.02

Topic: G.01. Appetitive and Aversive Learning

Support: Intramural Research Program ZIAMH002798

Title: Neural mechanisms reflecting aversive Pavlovian learning at ultra-high field (7T)

Authors: ***A. X. GORKA**[1], R. T. PHILIPS[1], S. TORRISI[3], A. MANBECK[4], M. GOODWIN[4], M. ERNST[5], C. GRILLON[2];
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Abstract: Learning how stimuli in the environment signal danger or safety is crucial for adaptive behavior. Within the framework of computational models of associative learning, prediction error reflects the difference between the experienced outcome and the outcome predicted by associative history. Evidence from animal models demonstrates that the periaqueductal gray matter (PAG) signals prediction errors during aversive Pavlovian learning. However, limited research has addressed whether the PAG reflects prediction errors within the human brain owing to the limited spatial resolution of conventional fMRI. Here we set out to address this question using ultra-high field neuroimaging (7-Tesla fMRI), which provides increased spatial resolution and an opportunity to examine the functional architecture of small neural structures. Forty-nine participants (22 women, mean age = 26.71) underwent habituation, acquisition, and extinction paradigms within the scanner environment. Male faces depicting fear were used as conditioned stimuli and electrodermal activity served as measures of conditioned responses. Repeated measure analyses demonstrated that the CS+ elicited enhanced phasic skin conductance responses compared to the CS- during acquisition, and that this effect was significantly reduced during extinction. Additionally, paired T tests demonstrate that neural responses during acquisition reflected enhanced activity to the CS+ within the dorsal anterior cingulate, thalamus, anterior insula, and PAG. Repeated measure ANOVA models further demonstrated that increased neural responses to the CS+ within the dorsal anterior cingulate and anterior insula were reduced during extinction. Lastly, axiomatic tests were conducted to determine whether BOLD responses within the PAG reflect prediction error signals. Together, these results shed light on the neural circuitry underlying the acquisition and extinction of aversive Pavlovian associations and can serve as a bridge between animal models and research investigating the neural mechanisms that process signals of danger or safety within the human brain.

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Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

Location: Room S104

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Presentation Number: 194.03

Topic: G.01. Appetitive and Aversive Learning

Support: Universidad de los Andes
Universidad Nacional de Colombia

Title: Amygdaloid and collicular electrical activity during the acquisition of a visual fear conditioning in anesthetized rats

Authors: *M. A. CARDENAS[1], A. MÚNERA[1], M. ROJAS[1], F. P. CÁRDENAS[2];
[1]Univ. Nacional De Colombia, Bogotá, Colombia; [2]Univ. De Los Andes, Bogotá, Colombia

Abstract: The superior colliculus (SC) is involved in visual perception mainly for contrast and quick movement information. These two features are crucial for the rapid response to a changing environment and can trigger emotional reactions. The SC send indirect projections to the basolateral nucleus of the amygdala (BLA; Linke, et al., 1999). This circuit seems to be relevant for visual fear reactions, but its role is not precisely known. Here we report the characterization of visual event related potentials (ERP) in both SC and BLA before and after a visual fear conditioning in anesthetized rats. Six male Wistar rats (380g) were anesthetized with Urethane 25% (1.5ml/Kg) and Xylazine (10mg/Kg). Recording electrodes were bilaterally placed in SC (AP=2.7; ML±1.5; DV=33.2) and BLA (AP=5.2; ML±5.4; DV=7.0). Twenty minutes later collicular and amygdaloid event related potential (baseline; 100 events) were obtained in response to a visual stimulus (20ms white light flash). After that a standard procedure for visual/aversive conditioning was done by pairing (100 trials) the same flash (conditioned stimulus) with an electrical shock (0,7mA; 1 second - unconditioned stimulus) delivered to the whiskers pad. Our results showed a change in the visual evoked response for both SC and BLA after the visual aversive conditioning (100 events). This change in the visual evoked response indicates an amygdaloid electrical response compatible with the acquisition of a conditioned fear response. After 300 presentations of the conditioned stimulus, in the absence of the unconditioned (extinction protocol) a decrease in the evoked response was found but nat a total suppression. In conclusion, this classical conditioning amygdaloid effect under anesthesia seems to be a promissory methodology for the systematic study of the role of the circuit SC-amygdala in the mediation of fear acquisition and the role of related structures.

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Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

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Presentation Number: 194.04

Topic: G.03. Emotion

Support: This research is supported by Cornell University Department of Design and Environmental Analysis graduate student dissertation funding.

Title: Electroencephalograph source network dynamics during emotion transitions

Authors: ***Y. HAO**, L. YAO, G. W. EVANS;
Cornell Univ., Ithaca, NY

Abstract: Emotions are dynamic yet emotion regulation is typically assessed in terms of a static emotional state. How do people regulate dynamic emotional changes as they respond to the demands of varying situations? We investigated emotion regulation during dynamic shifts in emotional contexts along with individual differences in emotion regulation style and chronic stress.

EEG source was estimated with Linearly Constrained Minimum Variance (LCMV) based beamforming algorithm. The imagery part of the coherence was used to estimate functional connectivity between estimated sources to construct the source network, involving the prefrontal cortex, anterior cingulate cortex, anterior insula, amygdala, hippocampus, parietal cortex, and occipital cortex. The EEG from 32 healthy participants were collected by a 128 channel Biosemi while viewing emotional image sequences changing from neutral to negative or from negative to neutral valence with standard stimuli (IAPS). Participants either passively watched the emotion sequences (control) or cognitive reappraised the negative stimuli. Individual differences in everyday use of reappraisal strategy and chronic stress were assessed. When images changed from neutral to negative, cognitive reappraisal decreased network activity (sum of coherence) among people with high chronic stress ($R = -0.51$, $p = .003$) and increased network strength for people with more cognitive reappraisal tendency ($R = 0.63$, $p = .0001$). When images changed from negative to neutral, the trend was reversed but with less statistical significance. Notably, the network change was more dominant in the left hemisphere when assessing daily cognitive reappraisal influence, whereas it was more dominant in the right hemisphere when assessing chronic stress influence. The results indicate that adaptation to event fluctuation relates to network flexibility moderated by individual differences factors.

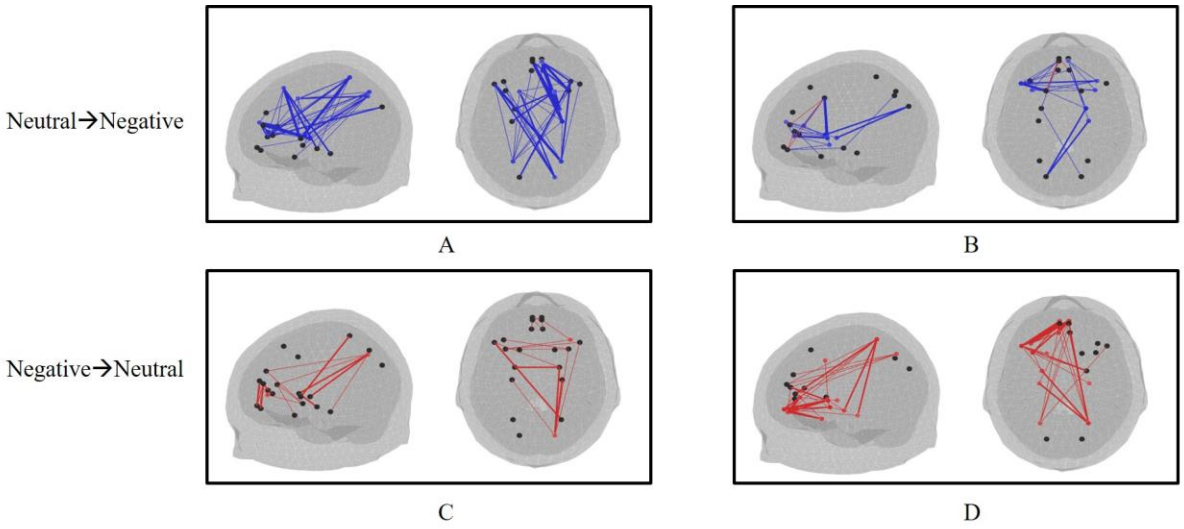

Figure 1. The correlation of the change of EEG source network with chronic stress (A and C) or cognitive reappraisal tendency (B and D). The blue line indicates negative correlation and red link indicates positive correlation. All pairwise links have $p < .05$. The thicker the line the higher the correlation.

Disclosures: **Y. Hao:** None. **L. Yao:** None. **G.W. Evans:** None.

Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

Location: Room S104

Time: Sunday, October 20, 2019, 1:00 PM - 2:45 PM

Presentation Number: 194.05

Topic: H.01. Animal Cognition and Behavior

Support: NIH Innovator DP2 DK105570
NIH R01 DK109930
NIH T32 5T32DK007516
Dauten HBI 01028681

Title: Reactivation of salient experiences in association cortex links cues to outcomes

Authors: ***A. U. SUGDEN**[1], L. A. SUGDEN[2], K. L. MCGUIRE[3], J. D. ZAREMBA[1], A. LUTAS[1], R. N. RAMESH[3], O. ALTURKISTANI[1], K. K. LENSJØ[1], C. R. BURGESS[1], M. L. ANDERMANN[1];
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Abstract: Learning from sensory experiences requires linking cues to diverse, often delayed outcomes. Experiences of cues and outcomes activate brain-wide patterns of neurons. During subsequent quiet periods, memories of recent experiences may become consolidated via

synchronous reactivation of these patterns throughout sensory cortex, amygdala, and hippocampus. A key hub that links these areas is lateral sensory association cortex, a region necessary for offline memory consolidation and recall of cue-outcome associations. Recently, human neuroimaging studies reported preferential reactivation of salient experiences in lateral visual association cortex. Here, we examined how reactivation of specific cue representations in association cortex neurons might link representations of cues and salient outcomes during gradual learning of a sensory task. We imaged hundreds of neurons across weeks as head-fixed mice learned to discriminate between visual cues predicting appetitive, aversive, or neutral outcomes. We observed distinct patterns of neurons that responded to each visual cue during the task, and these same patterns were subsequently reactivated during quiet waking in darkness. To identify these reactivation events, we developed a novel classifier that could accurately identify each cue presentation from momentary patterns of single-trial population activity, as well as subsequent, similar patterns in darkness. Neurons encoding food cues were often reactivated synchronously with neurons encoding the delivery or anticipation of rewards. Reactivation rates were higher following low-performance sessions and were also higher for food-predicting cues than for neutral cues, consistent with a role for cue reactivations in associative learning. At a circuit level, upon participation in food-cue reactivations, reward-related ensembles of cortical neurons increased their next-day functional connectivity with the local network, while other ensembles decreased their connectivity. We suggest that joint cortical reactivation of cue and outcome representations provides a substrate for consolidation of cue-outcome associations.

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Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

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Presentation Number: 194.06

Topic: G.03. Emotion

Support: National Natural Science Foundation of China Grant 31671116 J.T.
National Natural Science Foundation of China Grant 31761163005 J.T.
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NSFC 81425010 L.W.
International Big Science Program Cultivating Project of CAS Grant No.172644KYS820170004

Title: A new GABAergic somatostatin projection from the anterior BNST onto accumbal parvalbumin neurons controls anxiety

Authors: *Q. XIAO[1], X. ZHOU[1], P. WEI[1], L. XIE[1], B. WU[2], Y. HAN[1], J. WANG[3], A. CAI[3], F. XU[3], F. YANG[1], J. TU[1], L. WANG[1];
[1]Shenzhen Inst. of Advanced Technology, CAS, Shenzhen, China; [2]Dept. of Information Technol. and Electrical Engineering, ETH Zurich, Zurich, Swaziland; [3]Wuhan Inst. of Physics and Mathematics, CAS, Wuhan, China

Abstract: The prevail view is that parvalbumin (PV) interneurons play their modulation roles through local medium spiny projection neurons (MSNs) in emotional response. Here, we show that PV activity within the nucleus accumbens shell (sNAc) is directly required for producing avoidance when mice approach anxiogenic situations; $sNAc^{PV}$ neurons exhibited high excitability in chronically stressed models which displayed excessive maladaptive avoidance in an anxiogenic context. A new GABAergic somatostatin (SOM) afferent from the anterior dorsal bed nuclei of stria terminalis (adBNST) was uncovered which directly innervates $sNAc^{PV}$ neurons; optogenetic activation of this GABAergic terminals in sNAc produced an anxiolytic effect; activation of inhibitory inputs from aBNST to sNAc rescued the excessively anxious state on the stressed mice.
Our findings trigger new thinking about the nature and necessity of the link between the brain stress response region and reward circuitry component and, provide a new neurobiological basis for therapeutic interventions in pathological anxiety.

Disclosures: Q. Xiao: None. **X. Zhou:** None. **P. Wei:** None. **L. Xie:** None. **B. Wu:** None. **Y. Han:** None. **J. Wang:** None. **A. Cai:** None. **F. Xu:** None. **F. Yang:** None. **J. Tu:** None. **L. Wang:** None.

Nanosymposium

194. Cortical and Subcortical Mechanisms of Aversive Processing

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Presentation Number: 194.07

Topic: G.03. Emotion

Support: NIDA Grant DA041781
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BBRF NARSAD Independent Investigator (JAM)

Title: Dissecting the accumbal dynorphinergic projections underlying the emotional component of pain

Authors: *N. MASSALY[1], H. YOON[1], T. MARKOVIC[1], J. MORON-CONCEPCION[2];
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Abstract: Pain is a multifaceted experience composed of both a nociceptive/sensory and an emotional factor. Despite this dichotomy of persistent pain, current pharmacotherapies and preclinical pain studies mainly focus on relief of hyperalgesia and allodynia. While the acute nociceptive component of pain can be properly managed with prescription opioids, the untreated negative affect can lead to comorbid psychiatric disorders such as anxiety, depression, and opioid misuse when pain persists over time. In order to address the development of such comorbidities, preclinical studies have recently started to dissect the neurocircuitry of the aversive and emotional component of pain. In this line of thought, we recently demonstrated that inflammatory pain recruits the dynorphin kappa opioid receptor system in the Nucleus Accumbens to drive negative affective states. While inhibiting dynorphin-containing neurons in the nucleus accumbens fully reverses pain-induced negative affective states, the precise dissection of their synaptic projections, and their individual roles in driving negative affect, remains to be determined. In the present study we used viral approaches to uncover the projections of nucleus accumbens shell dynorphin neurons. Using a combination of optogenetics and a battery of behavioral tests, we further assessed the involvement of these dynorphinergic projections in driving negative affective states and co-morbid disorders. Altogether, this study implements our understanding of the circuitry responsible for the emotional component of pain, and may help us define new druggable targets to mitigate the development of pain comorbidities.

Disclosures: N. Massaly: None. **H. Yoon:** None. **T. Markovic:** None. **J. Moron-Concepcion:** None.

Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

Location: Room S402

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 195.01

Topic: H.02. Human Cognition and Behavior

Support: NIA/NIH R00 AG047334

Title: Hippocampal tract integrity relates to hippocampal memory-related activity: A combined dti-fmri study

Authors: *J. L. KLIPPENSTEIN[1], A. VENKATESH[2], A. ALCARAZ-TORRES[1], I. J. BENNETT[1];
[1]Dept. of Psychology, [2]Neurosci. Grad. Program, Univ. of California, Riverside, Riverside, CA

Abstract: Differentiating between similar and repeated events is a fundamental component of episodic memory. Across the lifespan, this mnemonic discrimination ability has been separately related to 1) better integrity of white matter tracts emanating from hippocampus (e.g., cingulum, fornix) and 2) hippocampal functional activity. However, no studies have directly related hippocampal track integrity and hippocampal activity during episodic memory performance. Moreover, the few studies that have assessed structure-function relationships outside of hippocampus have revealed mixed results, which may be due to comparisons between non-adjacent brain regions. Here, we assess the relationship between integrity of white matter tracts emanating from hippocampus and mnemonic discrimination related-activity in hippocampus. We collected diffusion tensor and functional magnetic resonance imaging data while 38 younger (mean age = 20.1 ± 1.7 years; 24 males) and 39 older (mean age = 73.5 ± 5.6 years; 13 males) healthy adults performed the Mnemonic Similarity Task. In the incidental study phase, participants viewed a series of to-be-remembered objects. In the test phase, participants made "old"/"new" judgments to a series of probe objects that were either repetitions from the memory set, similar to objects in the memory set, or novel. White matter integrity (fractional anisotropy, FA; mean diffusivity, MD) was extracted using an anatomical tract-of-interest approach and hippocampal activity was measured using a contrast between similar and repeated objects. Consistent with previous work, we found that across age groups 1) better cingulum and fornix integrity (higher FA) related to better mnemonic discrimination performance and 2) hippocampal activity was significantly different between similar and repeated objects. Extending previous work, we found that higher cingulum FA and lower fornix MD related to greater mnemonic discrimination related-hippocampal activity, independent of age. The current findings demonstrate that better integrity of white matter tracts emanating from hippocampus is associated with greater hippocampal memory-related activity, laying the groundwork for future investigations of these structure-function interactions in relation to aging and memory performance.

Disclosures: J.L. Klippenstein: None. **A. Venkatesh:** None. **A. Alcaraz-Torres:** None. **I.J. Bennett:** None.

Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

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Presentation Number: 195.02

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Council UK
National Institute of Mental Health, Besthesda, USA
Swiss League Against Epilepsy
University College London Child Health Research Trust

Title: Structural 3T MRI investigation of hippocampus subfields and amygdala nuclei in patients with developmental amnesia

Authors: *L. J. CHAREYRON[1], F. BASTOS[1], S. BUCK[1], R. C. SAUNDERS[3], M. MISHKIN[4], D. G. GADIAN[2], F. VARGHA-KHADEM[1];
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Abstract: An early-life episode of hypoxia-ischemia can damage the hippocampus that supports declarative memory and leads to developmental amnesia (DA). Patients with DA exhibit severe episodic memory impairment and largely preserved semantic memory. While bilateral hippocampal atrophy has long been reported in this patient group, examination at the level of the hippocampal subfields has not been reported as yet. Also, the impact of early-life hypoxic-ischemic episodes and/or hippocampal damage on the interconnected amygdala needs to be evaluated. Here we have used 3-Tesla MRI acquisitions to estimate hippocampal subfields and amygdala nuclei volumes in 8 patients with DA (age range: 8y-40y) and 8 controls (age range: 8y-18y). Our estimates revealed that the different hippocampal subfields were differentially affected by the early-life hypoxic-ischemic episodes. The two hippocampal regions defined as DG/CA3 and CA2/CA1 were more than 40% smaller in patients with DA than in controls, after correction for brain volume. Also, the Subiculum/Presubiculum/Parasubiculum region was 33% smaller in DA. In striking contrast, the volume of the uncus, the most anterior part of the hippocampus, was only 12% lower in patients with DA and not significantly different from controls. The possible low sensitivity of the uncus to early-life hypoxic-ischemic events could be linked to the differential vascularization of this region as compared to the rest of the hippocampus. Our estimates also revealed that the amygdala was not affected by hypoxic-ischemic episodes and/or associated hippocampal damage. The lateral, basal, accessory basal and remaining amygdala nuclei did not show any sign of atrophy in patients with DA. Interestingly, the volume of the amygdala was significantly correlated with the volume of the uncus in both control and DA groups, in contrast to other hippocampal regions. The amygdala receives substantial inputs from the uncus that, in turn, receives amygdala projections. Thus, in the absence of severe atrophy of the uncus, the functional interaction between the amygdala and the anterior remnant of the hippocampus could be, at least in part, preserved in patients with DA. Given the relative integrity of the uncus in patients with DA and its direct connections with the amygdala which in turn are preserved, the present findings raise the possibility that emotionally valenced episodic memories may be more accessible to recall than those with neutral emotional valence.

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Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

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Presentation Number: 195.03

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant RO1MH60941
NIA Grant F32AG059341

Title: Modulation of hippocampal brain networks produces changes in episodic simulation and divergent thinking

Authors: *P. P. THAKRAL[1], K. P. MADORE[2], S. E. KALINOWSKI[1], D. L. SCHACTER[1]; [1]Harvard Univ., Cambridge, MA; [2]Stanford Univ., Stanford, CA

Abstract: Episodic memory (the ability to remember specific past experiences), and the neural processes that support it, are engaged during tasks that extend beyond simple remembering, such as episodic simulation (the ability to imagine specific future experiences) and divergent thinking (the ability to generate creative ideas by combining diverse types of information). For example, functional magnetic resonance imaging (fMRI) studies indicate that a core network of brain regions, including the hippocampus, is jointly recruited during memory, simulation, and divergent thinking. However, because fMRI data are correlational, it is unknown whether activity increases in the hippocampus, and the core network more broadly, play a causal role in episodic simulation and divergent thinking. Here we employed fMRI-guided transcranial magnetic stimulation (TMS) to assess whether temporary disruption of hippocampal brain networks impairs both episodic simulation and divergent thinking. For each of two TMS sessions, continuous theta-burst TMS was applied to either a control site (vertex) or to a left angular gyrus target region. Critically, the target region was identified on the basis of a participant-specific resting-state functional connectivity analysis with a hippocampal seed region previously associated with episodic memory, episodic simulation, and divergent thinking. Following application of TMS, participants underwent fMRI and performed three tasks. In each task, participants were shown an object word and either imagined a related personal event in the next few years (episodic simulation task), generated creative and unusual uses of the object (divergent thinking task), or generated associated items and their definitions (non-episodic control task). Results demonstrated that, compared with TMS to the vertex, TMS to the target region reduced the number of episodic details (i.e., who, what, when, and where details comprising imagined events) produced for the simulation task and the number of creative uses produced for the divergent thinking task. By contrast, performance in the non-episodic control task did not statistically differ as a function of TMS site. Analysis of the fMRI data revealed that the decrease in behavioral performance was linked to a selective reduction in hippocampal activity during episodic simulation and divergent thinking following TMS to the target region compared with TMS to the vertex. Our findings are the first to indicate that hippocampal-targeted TMS can specifically modulate episodic simulation and divergent thinking and suggest that the hippocampus supports a common and critical process during these cognitive functions.

Disclosures: **P.P. Thakral:** None. **K.P. Madore:** None. **S.E. Kalinowski:** None. **D.L. Schacter:** None.

Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

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Presentation Number: 195.04

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 MH112357 to Uri Hasson and Kenneth A. Norman
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James S McDonnell Scholar Award to Morgan D. Barense
Sloan Research Fellowship to Christopher J. Honey

Title: Temporal integration of narrative information in a hippocampal amnesic patient

Authors: *X. ZUO[1], C. J. HONEY[1], M. D. BARENSE[2], D. CROMBIE[3], K. A. NORMAN[4,5], U. HASSON[4,5], J. CHEN[1];
[1]Dept. of Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]Dept. of Biol. II - Neurobio., Ludwig Maximilian Univ. of Munich, Munich, Germany; [4]Princeton Neurosci. Inst., [5]Dept. of Psychology, Princeton Univ., Princeton, NJ

Abstract: MOTIVATION. People with hippocampal damage can be profoundly impaired in recalling information from a different topic of discussion just 10 seconds ago. Meanwhile, these amnesic individuals often retain near-normal recall for prose passages (Baddeley & Wilson, 2002), and their memory deficits are rarely noticeable in everyday conversation. How is this possible? We hypothesized that amnesic patients might be able to integrate coherent patterns of information over minutes, relying on cortical regions with long-timescale capacity. BEHAVIOR. An amnesic patient (DA) with bilateral medial-temporal lobe damage (Rosenbaum et al., 2008) and healthy controls listened to narrative stimuli of different lengths (sentences, paragraphs) and semantic consistency (coherent, incoherent), followed by immediate verbal recall. For stimuli longer than two sentences, DA performed significantly worse than controls, consistent with the idea that the hippocampus supports long-term rather than short-term verbal recall. fMRI. 36 control subjects listened to a 7-minute story ("Pieman") while being scanned; another 18 subjects listened to a paragraph-scrambled version of Pieman (data from Simony et al., 2016). DA listened to both intact and scrambled Pieman. To directly compare the intact and scrambled conditions, we reordered subjects' paragraph-scrambled BOLD responses to match the intact

story's presentation order. We calculated spatial pattern inter-subject correlation (pISC) to measure neural response reliability between a) controls, and b) controls and patient, using a resting-state parcellation (Schaefer et al., 2018). For the intact story, DA's brain activity patterns were significantly similar to controls throughout auditory and some default network regions (IPL, PMC), suggesting that his experience of the coherent story resembled that of controls'. Interestingly, patient-vs-control pISC in IPL did not decrease over time, suggesting that event boundaries in the story did not disrupt DA's coherent experience. In his IPL, intact-vs-unscrambled pISC was lower than intact pISC, indicating this region's sensitivity to the scrambling manipulation and supporting the notion that it carries information across multiple paragraphs. CONCLUSION. Attempts to probe amnesic patients' continuous experience have often been difficult, as the act of asking questions introduces a discontinuity and hinders their recall of events before the breakpoint. We observed neural responses consistent with a continuous integration of information over tens of seconds, suggesting that patients may be able to maintain coherent mental contexts in their experience of the world.

Disclosures: **X. Zuo:** None. **C.J. Honey:** None. **M.D. Barense:** None. **D. Crombie:** None. **K.A. Norman:** None. **U. Hasson:** None. **J. Chen:** None.

Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

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Topic: H.02. Human Cognition and Behavior

Support: The Wellcome Centre for Human Neuroimaging is supported by core funding from the Wellcome Trust (203147/Z/16/Z).

Title: Neural signatures of perceptual predictions emerge concurrently in hippocampus and visual cortex during learning

Authors: *F. AITKEN, P. A. CABILES, P. KOK;
UCL, London, United Kingdom

Abstract: The complex, noisy and ambiguous stream of inputs constantly presented to our senses is replete with statistical regularities that can help us process them. For instance, hearing a particular jingle will prime our sensory systems for the sight (and taste!) of ice cream. Recent studies have suggested that the hippocampus, a canonical memory system, may be able represent expected visual shapes on the basis of predictive cues. However, it is currently unclear how the brain acquires such predictive associations, and whether hippocampal prediction signals are directly related to processing improvements in visual cortex. Here, we exposed human participants (N=24) to complex auditory cues (i.e., sequences of five tones) that predicted which

of two complex abstract shapes (Fourier descriptor objects) would be presented. We measured brain activity using high-resolution functional magnetic resonance imaging (fMRI), and used multivoxel pattern analysis to study representations of (presented and predicted) complex shapes in both hippocampus and visual cortex. During each block of 32 trials, two new auditory cues were presented (16 trials per cue), each of which predicted the appearance of one of the two shapes with 75% validity. Participants were not informed about the predictive relationship between the cues and shapes, and were asked to perform an orthogonal discrimination task on the visual shapes. Debriefing confirmed that they were not aware of the predictive value of the auditory cues. Strikingly however, the pattern of activity in the hippocampus started reflecting these predictive relationships in the second half of the blocks. Specifically, over time hippocampus activity started to resemble a prediction error signal: only unexpected shapes that violated the prediction evoked by the cues were represented. At the same time, visual cortex showed a canonical signature of expectation modulation: expectation suppression. That is, shapes that were predicted by the cues evoked less activity than those that violated the cue predictions, a phenomenon that has been suggested to reflect more efficient processing of expected stimuli. The time courses with which predictive signals emerged in hippocampus and visual cortex were strikingly similar, suggesting a functional link between the two. Altogether, these results suggest an important role for the hippocampus in guiding processing in visual cortex.

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Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

Location: Room S402

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 195.06

Topic: H.02. Human Cognition and Behavior

Support: DFG grant GA730/3-1

Title: Rehearsal initiates systems memory consolidation, sleep makes it last

Authors: L. HIMMER[1], ***M. SCHÖNAUER**[2], D. HEIB[3], M. SCHABUS[3], S. GAIS[1];
[1]Inst. für Medizinische Psychologie, Tübingen, Germany; [2]Princeton Univ., Princeton, NJ;
[3]Univ. of Salzburg, Salzburg, Austria

Abstract: After encoding, memories undergo a transitional process termed systems memory consolidation. It allows fast acquisition of new information by the hippocampus, as well as stable storage in neocortical long-term networks, where memory is protected from interference. Whereas this process is generally thought to occur slowly over time and sleep, we recently found a rapid memory systems transition from hippocampus to posterior parietal cortex (PPC) that

occurs over repeated rehearsal within one study session. Here, we use fMRI to demonstrate that this transition is stabilized over sleep, whereas wakefulness leads to a reset to naïve responses, such as observed during early encoding. The role of sleep therefore seems to go beyond providing additional rehearsal through memory trace reactivation, as previously thought. We conclude that repeated study induces systems consolidation, while sleep ensures that these transformations become stable and long lasting. Thus, sleep and repeated rehearsal jointly contribute to long-term memory consolidation.

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Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

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Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 195.07

Topic: H.02. Human Cognition and Behavior

Title: Posterior-anterior gradient in medial temporal lobe reactivation of details vs. gist

Authors: S. SELVAM, R. P. COLEMAN, K. MATTINGLY, W. B. CORLEY, M. IBRAGIMOVA, *N. C. HINDY;
Univ. of Louisville, Louisville, KY

Abstract: Upon meeting someone new, we rapidly encode both the specific details and overall gist of the event. Recent studies demonstrate that medial temporal lobe (MTL) reactivation is predictive of subsequent memory of individual events (Staresina et al, 2013 PNAS). How are memories of details and gist of individual events simultaneously encoded? To examine the relationship between offline reactivation and the encoding of details vs. gist, we combined the reactivation paradigm from Staresina and colleagues with a behavioral paradigm designed to induce false memories of non-presented gist words (Roediger and McDermott, 1995 JEP). During high-resolution fMRI, participants listened to lists of semantically related words that were each spoken in either a male or female voice. After every five lists, participants performed a simple number judgement task during a brief delay period followed by a recognition test with confidence ratings, which included words from the encoding phase mixed with the non-presented gist words and unrelated distractors. If a participant indicated that a word was “old”, they were asked to rate their confidence in judging the gender of the voice in which the word was presented. We replicate previous findings of false memory effects, showing that participants were nearly as confident that the gist words were previously presented as they were about the presented words. Using multivariate pattern analysis, we measured pattern reactivation of each preceding list during the delay period. Reactivation in anterior hippocampus and MTL cortex during the delay predicted participants’ confidence that the corresponding gist words had been

presented. At the same time, reactivation in posterior hippocampus predicted confidence in recognition and source memory of presented words. Findings link offline MTL reactivation to the formation different components of episodic memory, suggesting that multiple levels of episodic detail may be differentially encoded along the long axis of the hippocampus.

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Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

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Presentation Number: 195.08

Topic: H.02. Human Cognition and Behavior

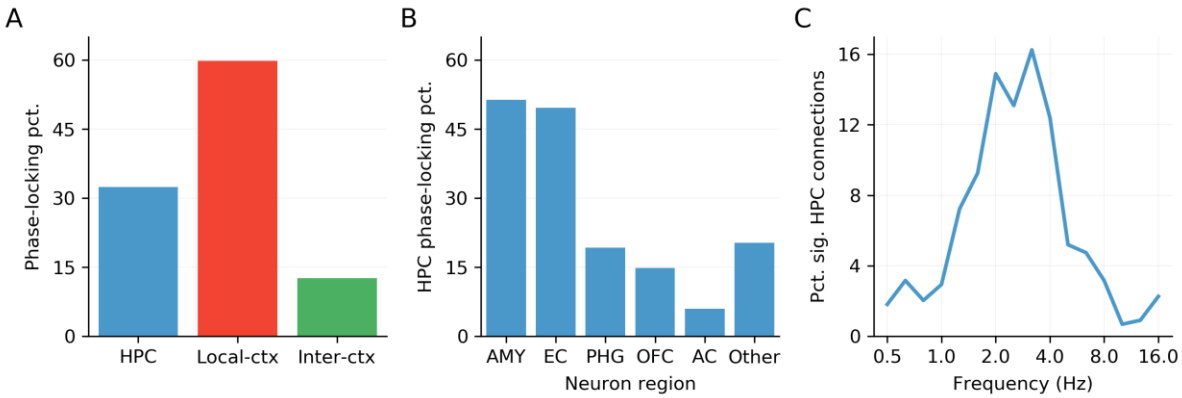
Support: NIH Grant MH061975

Title: Human cortical neurons phase-lock to hippocampal theta

Authors: *D. R. SCHONHAUT, E. A. SOLOMON, N. A. HERWEG, T. D. PHAN, M. J. KAHANA;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Rationale: Although disrupted connectivity between cortex and the hippocampus (HPC) predicts episodic memory dysfunction, we do not understand how these regions normally communicate. In rodents, phase-locking between cortical neurons and HPC theta oscillations facilitates information transfer to the HPC and supports memory-guided behavior. Here, we explored a role for HPC phase-locking in the human brain.
Methods: We recorded cortical neurons (N=1250) and HPC local field potentials from intracranial microwires in 18 epilepsy patients who played a laptop navigation game. We assessed phase-locking for all ipsilateral connections between cortical cells and HPC electrode bundles, calculating the mean vector length of spike phases for oscillations from 0.5 to 16 Hz (16 log-spaced wavelets) and selecting, for each connection, the frequency with maximum mean vector length. To determine significance, we obtained surrogate distributions by randomly circularly shifting spike trains, then set a strict 5% false discovery rate across comparisons.
Results: We found significant phase-locking for 32.4% of the 1367 connections between cortical neurons and HPC oscillations. HPC phase-locking occurred maximally in the 2-4 Hz slow theta range and most commonly for cells in the amygdala and entorhinal cortex. Cortical neurons phase-locked to the HPC at lower rates than to local oscillations (59.8%) but at higher rates than to intercortical oscillations, on average (12.6%). Notably, 45.4% of significant HPC phase-locking occurred at a frequency at which local phase-locking was insignificant, demonstrating these effects were independent.

Conclusions: We describe the first cellular measure of cortico-HPC connectivity in the human brain. While prior studies have found that HPC theta can organize local neural activity during episodic memory tasks, our results provide a direct link between HPC theta and remote, cortical firing. HPC phase-locking could be an important mechanism through which cortical regions communicate with the HPC to guide the encoding and retrieval of episodic memories.



Disclosures: D.R. Schonhaut: None. **E.A. Solomon:** None. **N.A. Herweg:** None. **M.J. Kahana:** None. **T.D. Phan:** None.

Nanosymposium

195. Medial Temporal Lobe in Learning and Memory

Location: Room S402

Time: Sunday, October 20, 2019, 1:00 PM - 3:15 PM

Presentation Number: 195.09

Topic: H.02. Human Cognition and Behavior

Support: US-Israel Binational Foundation Grant no. 2017015

Title: Hippocampal ripples linked to encoding and free retrieval of visual episodic memories in the human brain

Authors: *Y. NORMAN[1], E. M. YEAGLE[2,3], S. KHUVIS[2,3], M. HAREL[1], A. D. MEHTA[2,3], R. MALACH[1];
[1]Neurobio., Weizmann Inst. of Sci., Rehovot, Israel; [2]Neurosurg., Feinstein Inst. for Med. Res., Manhasset, NY; [3]Donald and Barbara Zucker Sch. of Med. at Hofstra/Northwell, Manhasset, NY

Abstract: Hippocampal Sharp Wave Ripples (SWRs) constitute one of the most synchronized activation events in the brain. During a ripple, 10-15% of pyramidal neurons in the hippocampal-entorhinal output pathway discharge synchronously (Mizuseki and Buzsáki, 2013), orchestrating a massive network activation that has a potent impact on a variety of cortical and subcortical targets (Joo and Frank, 2018; Logothetis et al., 2012). While extensive research has

demonstrated the likely role of ripples in offline memory consolidation - their content and function during awake, conscious cognition remains unclear. Here, we directly examined this question using intra-cranial EEG recordings in fifteen epilepsy patients engaged in free recall of previously viewed photographs. A unique advantage of intracranial EEG recordings conducted in patients is that the diagnostic procedure calls for multiple simultaneous recording sites in each patient, while allowing on-line self-reporting of the patient's inner cognitive contents. Here we simultaneously recorded, on the one hand, LFP and SWR activity in the hippocampus, and on the other hand, high-frequency broadband signal (HFB; 60-160Hz) - reflecting local spiking activity - in task relevant, content-specific, cortical sites. This offers the opportunity to uncover the dialogue between the hippocampal SWRs and the cortex during various cognitive events that occur during free recall. Our results reveal three major new aspects of SWRs function: First, they demonstrate a link between SWRs elicited during memory formation (i.e. picture viewing), and the likelihood of a certain picture to be freely recalled. Second, they reveal that SWRs increase their rate in a content-specific manner 1-2 seconds prior to the free recall event. Finally, they show that reinstatement of cortical activity during memory recall is preferentially time-locked to hippocampal SWR events. Together, our results demonstrate a content-specific link between hippocampal SWRs and verbally reported human episodic memory. The results point to a significant role for SWRs in both memory encoding and retrieval processes. We hypothesize that the SWRs set up an integrated dialogue between the hippocampus and content-selective cortical sites that enables the recall process to take place. These results extend the role of SWR to the domain of conscious human memory recall and to non-navigational tasks. Supported by US-Israel BSF grant to Mehta and Malach.

Disclosures: **Y. Norman:** None. **E.M. Yeagle:** None. **S. Khuvis:** None. **M. Harel:** None. **A.D. Mehta:** None. **R. Malach:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.01

Topic: A.01. Neurogenesis and Gliogenesis

Title: Single cell transcriptome analysis reveals the roles of tamoxifen in regulating cortical neurogenesis in prenatal and adult brains

Authors: *C. LEE[1], L. ZHOU[2], J. LIU[2], J. SHI[2], J. WANG[1], Y. GENG[2], X. SU[1], N. BARAD[1], Y. E. SUN[1], Q. LIN[1];
[1]UCLA, Los Angeles, CA; [2]Tongji Univ., Shanghai, China

Abstract: Prior evidence suggests prominent effects of tamoxifen exposure on overall embryonic development. Both our and prior studies have shown that tamoxifen administration by

both gavage and intraperitoneal injections to pregnant mice led to difficulty giving birth, which eventually requires caesarean derivation and fostering for pup survival. Currently, specific effects of tamoxifen on cortical neurogenesis are not well characterized. Nevertheless, tamoxifen induced creER-LoxP system is still a widely accepted method to track neural lineages and to study gene functions without accounting for potential effects from tamoxifen administration. Here, we report that prenatal tamoxifen exposure promoted precocious cortical neurogenesis, while inhibited ventricular zone progenitor proliferation. We show that the balance of developmental signaling is thrown off. Further, prenatal tamoxifen exposure had long-lasting effects on cortical neural lineage specification and neural circuitry integrity in adult offspring. In adult mice, administration of tamoxifen significantly attenuated adult neural progenitor proliferation in both SVZ and the hippocampus. Moreover, administration of tamoxifen at early stage of brain development inhibited gliogenesis in the corpus callosum of adult offsprings. In summary, this study demonstrates potential impacts of tamoxifen on neurogenesis, astrogliogenesis, and neural migration in both developing and mature brains, suggesting tamoxifen-induced CreER-LoxP system is not suitable for neural lineage tracing study in both embryonic and adult CNS.

Disclosures: **C. Lee:** None. **L. Zhou:** None. **J. Liu:** None. **J. Shi:** None. **J. Wang:** None. **Y. Geng:** None. **X. Su:** None. **N. Barad:** None. **Y.E. Sun:** None. **Q. Lin:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R00HD073269
NIH Grant R01NS096176
USC start-up

Title: Modeling microcephaly with cerebral organoids and mice reveals a WDR62-CEP170-KIF2A pathway promoting cilium disassembly in neural progenitors

Authors: *W. ZHANG, S. YANG, M. YANG, S. HERRLINGER, Q. SHAO, J. CHEN; USC, Los Angeles, CA

Abstract: Primary microcephaly is caused by mutations in genes encoding centrosomal proteins including WDR62 and KIF2A. However, mechanisms underlying human microcephaly remain elusive. By creating the first hypermorphic mutant allele, we previously reported that *Wdr62* deletion disrupts mitotic progression and leads to cell death of neural progenitor cells (NPCs) in mice (Nat. Commun., 2014). Here we generated a new *Wdr62* null mice and mutant human

cerebral organoids. We found that *WDR62* deletion resulted in a reduction in the size of mouse brains and organoids due to the disruption of NPCs, including outer radial glia (oRG). WDR62 ablation led to retarded cilium disassembly, long cilium, and delayed cell cycle progression leading to decreased proliferation and premature differentiation of NPCs. Mechanistically, WDR62 interacts with and promotes CEP170's localization to the basal body of primary cilium, where CEP170 recruits microtubule-depolymerizing factor KIF2A to disassemble cilium. WDR62 depletion reduced KIF2A's basal body localization, and enhanced KIF2A expression partially rescued deficits in cilium length and NPC proliferation. Thus, modeling microcephaly with cerebral organoids and mice reveals a WDR62-CEP170-KIF2A pathway promoting cilium disassembly, disruption of which contributes to microcephaly.

Disclosures: W. Zhang: None. **S. Yang:** None. **M. Yang:** None. **S. Herrlinger:** None. **Q. Shao:** None. **J. Chen:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant EY027003
NSF Grant IOS-1457126

Title: The non-clustered protocadherins interact with the Wnt receptor Ryk to control proliferation and neurogenesis

Authors: S. BISWAS[1], M. R. EMOND[2], S. LIGHT[3], M. MORROW[2], ***J. D. JONTES**[2]; [1]Dept. of Neurosci., [2]Ohio State Univ., Columbus, OH; [3]The Ohio State Univ., Columbus, OH

Abstract: The non-clustered protocadherins comprise a family of homophilic cell-cell adhesion molecules that are linked to a variety of neurodevelopmental disorders that include intellectual disability, autism spectrum disorders, schizophrenia and epilepsy. How mutations in these genes give rise to these disorders is not known. To explore their roles in neural development, we have made targeted lesions in several zebrafish protocadherins (*pcdh1a*, *pcdh7a*, *pcdh9*, *pcdh17*, *pcdh18b*and *pcdh19*). Using both *in situ*hybridization and BAC transgenesis, we find that these protocadherins are each expressed in neural progenitor cells, as well as neurons. Targeted disruption of these genes results in increased proliferation and neurogenesis, as shown both by staining for phospho-histoneH3 and direct counting of cell divisions in timelapse image sequences in BAC transgenic embryos. In addition, we show by co-immunoprecipitation that members of this family interact with the Wnt receptor Ryk, which has been shown to regulate neurogenesis in rodents. Loss of Ryk occludes the increased proliferation in protocadherin

mutants, revealing a functional interaction between protocadherins and Ryk. Our results reveal that the control of proliferation and differentiation is a core function of the non-clustered protocadherins and that they interact both physically and functionally with the Wnt-Ryk signaling pathway.

Disclosures: S. Biswas: None. **M.R. Emond:** None. **S. Light:** None. **M. Morrow:** None. **J.D. Jontes:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.04

Topic: A.05. Axon and Dendrite Development

Support: NIH Pioneer Award DP1 NS106665
Paul G. Allen Frontiers Group
Brain Research Foundation Scientific Innovations Award program
Human Frontier Science Program LT000561/2011-L
European Molecular Biology Organization ALTF 1360-2010

Title: Reciprocal axon interactions establish corticotopic pre-patterning of the developing corpus callosum

Authors: A. POULOPOULOS[1,2], *P. DAVIS[1], Y. ITOH[1], T. A. ADDISON[1], J. D. MACKLIS[1];
[1]Dept of Stem Cell and Regenerative Biology, and Ctr. for Brain Sci., Harvard Univ., Cambridge, MA; [2]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The corpus callosum is the largest white matter tract, which in humans carries 200 million axons across all areas of the cortex. The sorting and proper targeting of this massive number of connections poses a difficult neurodevelopmental problem. Here we examine the development and internal organization of the corpus callosum, and identify a molecular mechanism of early circuit development that informs callosal axons to their cognate projection targets in the contralateral cortex. Using mesoscale mapping of callosal projections we demonstrate that early callosal topography is contiguously corticotopic and pre-patterned during development independent from activity. Using ectopic transplantation experiments in perinatal mouse brains, we demonstrate that callosal axons project autonomously to their cognate target areas, indicating that internal molecular determinants lead to self-organization of early callosal pre-patterning. To identify the molecular mechanisms involved in this process, we performed newly developed two-color growth cone sorting and subcellular proteomics from distinct callosal projections, revealing that callosal cell adhesion molecules display distinct levels between areas.

To examine whether the quantitative levels of adhesion molecules provide information on the corticotopic position of individual projections, we manipulated *in vivo* the levels of the canonical axon adhesion molecule NCAM1, and observed corresponding shifts in the topographic projection field of manipulated axons. We present evidence that a mechanism by which matched levels of adhesion molecules between neighboring axons keep the developing callosum intrinsically organized throughout early circuit development. After midline crossing, transhemispheric callosal axon interactions engage to guide axons back to their cognate areas in the contralateral cortical grey matter. We propose that this mechanism of early circuit development might be generalizable across long-range reciprocal projections of the mammalian CNS.

Disclosures: A. Poulopoulos: None. **P. Davis:** None. **Y. Itoh:** None. **T.A. Addison:** None. **J.D. Macklis:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.05

Topic: A.05. Axon and Dendrite Development

Support: Brain Canada Foundation
Health Canada
Kids Brain Health Network
Fonds de recherche du Québec - Santé
Epilepsy Canada
Savoy Foundation
CURE Epilepsy

Title: *TRIO* loss-of-function impairs the tangential migration of GABAergic interneurons through RhoA hypoactivation and causes severe epileptic encephalopathy

Authors: *L. EID[1,2], L. FAUTEUX-LOISELLE[1,2], E. DOUET[1], X. JIANG[1,2], M. LACHANCE[1], S. TENE TADOUM[1,2], A. LUPIEN-MEILLEUR[1,2], F. CHARRON-LIGEZ[1,2], G. GODIN[1,2], P. TAMER[1,2], J.-C. LACAILLE[2], E. ROSSIGNOL[1,2];
[1]Ctr. De Recherche Du CHU Sainte-Justine, Montreal, QC, Canada; [2]Univ. de Montreal, Montreal, QC, Canada

Abstract: Recessive mutations in the *TRIO* gene are associated with intellectual deficiency (ID), autism spectrum disorder (ASD) and/or epileptic encephalopathies (EE). TRIO is a dual guanine nucleotide exchange factor (GEF) that activates Rac1 and RhoA. *Trio* has been shown to regulate dendritic development in excitatory neurons, pathfinding of thalamocortical and spinal

cord axons as well as the morphogenesis of developing cerebellar granule cells. However, its roles in GABAergic interneuron (IN) development are unknown. Given the central role of RhoA and Rac1 in cytoskeletal remodelling during neuronal migration and the implication of IN pathologies in ASD and EE, we hypothesized that *Trio* might be a central regulator of IN migration. We generated *Dlx5/6^{Cre};Trio$^{c/c}$;RCE^{EGFP}* mutant mice carrying a conditional deletion of *Trio* in GABAergic INs and investigated the prenatal impact of the targeted deletion of *Trio* on IN migration dynamics in medial ganglionic eminence (MGE) explants. We find a significant delay in tangential migration in *Trio* mutant mice at e13.5 and 15.5. Time-lapse imaging of e13.5 MGE explants cultured for 48h reveals impaired branching dynamics in mutant INs, as indicated by an increase in the growth cone splitting rate and number of neurites, compared to WT littermates. As a result, IN migration is slower, with less frequent nucleokinesis and a shortened net displacement, in mutants compared to WT littermates. Electroporation of an active RhoA, but not Rac1, completely rescues the *Trio*-associated morphological defects in GABAergic INs in cultured organotypic slices. Furthermore, electroporation of a mutated version of *Trio* cDNA lacking the GEFD1 or GEFD2 domain in *Trio*-repressed INs points toward a requirement of the GEFD2 domain for proper morphological development of INs. Finally, mice with a targeted deletion of *Trio* in GABAergic INs develop spontaneous tonic-clonic seizures by P14 and reduced cortical inhibition as shown by decreased IPSC frequency. Altogether, our data suggest that *TRIO* loss-of-function mutations impact the migration of cortical INs, disrupting the establishment of cortical inhibitory networks, and result in epilepsy, providing functional evidence for the implication of *TRIO* as a novel EE gene.

Disclosures: **L. Eid:** None. **L. Fauteux-Loiselle:** None. **E. Douet:** None. **X. Jiang:** None. **M. Lachance:** None. **S. Tene Tadoum:** None. **A. Lupien-Meilleur:** None. **F. Charron-Ligez:** None. **G. Godin:** None. **P. Tamer:** None. **J. Lacaille:** None. **E. Rossignol:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.06

Topic: A.05. Axon and Dendrite Development

Support: NSF 1146944-IOS
NSF 0951019-IOS
NIH 1R01MH094607-01A1
NIH R35 GM119785
DARPA D16AP00093

Title: Microtubule assembly is required for dynein-mediated microtubule translocation and neurite elongation

Authors: K. MCELMURRY[1], J. E. STONE[1], D. MA[2], P. LAMOUREUX[4], Y. ZHANG[3], F. HUANG[2], K. E. MILLER[4], ***D. M. SUTER**[1];
[1]Biol. Sci., [2]Weldon Sch. of Biomed. Engin., [3]Statistics, Purdue Univ., West Lafayette, IN; [4]Dept. of Integrative Biol., Michigan State Univ., East Lansing, MI

Abstract: Growth cones are highly motile sensory structures at the distal tips of elongating neurites. Previously, we have shown that bulk microtubule (MT) movement correlates with neurite elongation, and blocking either dynein activity or MT assembly inhibits both processes. However, whether the contributions of MT dynamics and dynein activity to neurite elongation are separate or interdependent is unclear. Here, we investigated the underlying mechanism by testing the roles of dynein and MT assembly in neurite elongation of *Aplysia* and chick neurites using time-lapse imaging, fluorescent speckle microscopy, super-resolution imaging, and biophysical analysis. Pharmacologically inhibiting either dynein activity or MT assembly reduced both bulk and individual MT anterograde translocation as well as neurite elongation rates. Suppressing both processes simultaneously had compensatory rather additive effects. Single-molecule switching nanoscopy revealed fewer dynein motors co-localized with MTs when MT assembly was inhibited. Lastly, the increase in neurite tension normally induced by dynein inhibition was abolished when MT assembly was blocked. Altogether, our results strongly suggest disruption of MT assembly blocks neurite outgrowth in part because it inhibits dynein-mediated bulk MT translocation.

Disclosures: K. McElmurry: None. **J.E. Stone:** None. **D. Ma:** None. **P. Lamoureux:** None. **Y. Zhang:** None. **F. Huang:** None. **D.M. Suter:** None. **K.E. Miller:** None.

Nanosymposium

265. Cell Biological Mechanisms of Neural Development

Location: Room S402

Time: Monday, October 21, 2019, 8:00 AM - 9:45 AM

Presentation Number: 265.07

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R01NS093200
Foundation For Prader-Willi Research Grant 533603

Title: Deciphering the molecular basis of neuronal development deficits in the recurrent genomic disorder

Authors: *D. J. TAI[1], S. ERDIN[1], K. MOHAJERI[1], X. NUTTLE[1], K. O'KEEFE[1], B. B. CURRALL[1], C. ZHANG[2], C. LEE[2], J. F. GUSELLA[1], M. E. TALKOWSKI[1];
[1]Ctr. for Genomic Med., Massachusetts Gen. Hosp., Boston, MA; [2]The Jackson Lab. for Genomic Med., Farmington, CT

Abstract: Reciprocal copy number variants (CNVs) of chromosome 16p11.2 (OMIM 611913) and 15q11.2-13.3 Prader-Willi syndrome (PWS), OMIM 176270 are ones of the most significant recurrent genomic disorders (RGDs) associated with intellectual disability and autism spectrum disorder. The mechanism of non-allelic homologous recombination (NAHR)-mediated CNV formation involves the mispairing of the flanking segmental duplications, which can result in either the loss or gain of the unique genic segment (600 kb in 16p11.2 RGD; 5.3 Mb in PWS RGD). However, the pathogenic mechanism and the functional relevance of individual genes within RGDs and the combined contributions of multiple genes are not known. To interrogate the region against an isogenic background, we developed a novel CRISPR/Cas9 genome engineering approach to efficiently generate reciprocal CNV that mimics NAHR (Tai et al., *Nature Neuroscience*, 2016). With the comprehensive cell models and the integrated molecular and computational approaches, we attempt to uncover the molecular basis for abnormal neurodevelopment in disease by recapitulating neuropathology of RGD in derivative neuron models. Our preliminary data and several recent studies have strongly suggested *KCTD13* might be one of the drivers of 16p11.2 RGD. We then defined cellular phenotypes, transcriptional signatures, and co-expression modules that are shared with 16p11.2 CNV models, and those that are unique to *KCTD13* heterozygous deletion (HET). Our transcriptome profilings and analyses showed that genes regulating cytoskeleton (GO:0005856) and translational initiation (GO:0006413) were significantly altered in the neurons with 16p11.2 CNV. Notably, the *SLC17A7* and *CAMK2A* genes regulating glutamate transport and neuronal plasticity are significantly altered in *KCTD13* HET and 16p11.2 CNV neurons. Also, the neurite dynamic experiments revealed increased neurite length in *KCTD13* HET and the neurons carrying 16p CNV. Interestingly, *KCTD13* HET neurons showed increased neuronal activity but the 16p CNV neurons displayed reduced neuronal activity, suggesting that distinct mechanisms may underlie neurite dynamics and neuronal activity. Regarding the ongoing PWS work, we aim to assess the global molecular effects and consequent transcriptional alterations associated with the disease. These studies will allow us to gain more insights into the relationship of gene expression to phenotype and the pathogenic mechanism underlying the disease. With multidimensional assessment, the causal molecular and cellular mechanisms and divergent and convergent transcriptional signatures in RGDs will be further evaluated.

Disclosures: D.J. Tai: None. **S. Erdin:** None. **K. Mohajeri:** None. **X. Nuttle:** None. **K. O'Keefe:** None. **B.B. Currall:** None. **C. Zhang:** None. **C. Lee:** None. **J.F. Gusella:** None. **M.E. Talkowski:** None.

Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.01

Topic: B.11. Glial Mechanisms

Support: ERC Starting Grant
Israel Science Foundation, Individual research grant
Canada-Israel grants (CIHR-ISF)

Title: Astrocytic manipulation impairs remote memory acquisition by specifically disrupting CA1 to ACC communication

Authors: *A. KOL, A. ADAMSKY, T. KREISEL, M. LONDON, I. GOSHEN;
The Hebrew Univ., Jerusalem, Israel

Abstract: Pioneering studies showed that astrocytes can sense and modify neuronal activity and thus modulate behavior, including cognitive function. In this work we examined the role of astrocytes in remote memory, and their ability to exert projection-specific effects on their neighboring neurons.
We employed chemogenetics to recruit Gi-mediated signaling in astrocytes using the designer receptor hM4Di, exclusively activated by CNO. Using 2-photon imaging of astrocytes co-expressing hM4Di and GCaMP we found reduced calcium levels and dynamics following CNO application. Gi-pathway activation in CA1 astrocytes during memory acquisition impaired remote, but not recent, contextual memory retrieval. To reveal the mechanisms underlying this unexpected result, we tested brain-wide neuronal activity following CA1 astrocytic modulation during memory acquisition, and found that it specifically decreased cFos levels at the anterior cingulate cortex (ACC), known to be involved in remote memory retrieval. This finding suggests that hippocampal astrocytes specifically modulate the activity of ACC-projecting neurons during memory acquisition. To examine this hypothesis, we first verified that CA1 astrocytic modulation is capable of affecting CA1-to-ACC communication. By dual in-vivo recordings from CA1 and ACC, we found that Gi pathway activation in CA1 astrocytes decreased the response of CA1 neurons to optogenetic Schaffer Collaterals stimulation, and diminished the downstream recruitment of the ACC. Finally, to directly test whether astrocytes can selectively prevent the recruitment of ACC-projecting CA1 neurons we tagged these projection neurons using a retro-AAV and measured their recruitment during memory acquisition by cFos expression. Indeed, activation of the Gi-pathway in CA1 astrocytes during memory acquisition specifically prevented the recruitment of ACC-projecting CA1 neurons, compared to the general population of CA1 pyramidal neurons.
Our results are the first to show a massive recruitment of ACC-projecting CA1 neurons during memory acquisition, necessary for remote (but not recent) memory, and reveal the ability of astrocytes to exert projection-specific effects on neurons.

Disclosures: A. Kol: None. **A. Adamsky:** None. **T. Kreisel:** None. **M. London:** None. **I. Goshen:** None.

Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.02

Topic: D.08. Visual Sensory-motor Processing

Support: Howard Hughes Medical Institute
Simons Collaboration on the Global Brain Awards (325171, 542943SPI)

Title: Evidence accumulation in astrocytes for behavioral state transitions

Authors: *Y. MU[1], Z. WEI[1], D. V. BENNETT[2], M. RUBINOV[3,1], S. NARAYAN[1], C.-T. YANG[1], M. TANIMOTO[1], B. D. MENSH[1], L. LOOGER[1], M. B. AHRENS[1];
[2]Ahrens Lab., [1]Janelia Res. Campus / HHMI, Ashburn, VA; [3]Vanderbilt Univ., Nashville, TN

Abstract: When actions consistently fail to produce their desired consequences, animals tend to 'give up' and enter a temporary state of passivity. For example, in the virtual environment, a larval zebrafish attempts to swim forward. If the swim does not lead to perceived movement, the fish behaves 'futility-induced passivity', which, shown in our previous study, is implemented through a cooperative mechanism of the noradrenergic system and brainstem radial astrocytes. Specifically, the noradrenergic system codes for behavioral failures, radial astrocytes accumulate these noradrenergic failure signals, encode them in calcium levels, and trigger passivity once calcium reaches a critical level. Here, we studied how radial astrocytes accumulate evidence that swimming is futile on single trials and across trials.
During sequences of successful and failed actions, times at which behavioral passivity was triggered depended on the probability that swim bouts were futile. Across trials, during swim attempts, astrocyte calcium levels reflected the probability of successful swim bouts in the temporal slope of calcium increase and in the calcium levels reached at plateau. On single trials, they integrated, bout-by-bout, the successes, failures, and absence of swimming by step-wise increases and decreases in calcium followed by a long-timescale leak to baseline, the amplitude of which follows a detailed manner of the computation between their effortness (swim power) and feedback on each single swim event. We present candidate upstream encoding circuits and downstream readout circuits. Thus, the fish-analogue of mammalian astrocytes performs evidence accumulation that can be tracked during individual behavioral events and represents the integrated futility of actions and thus form the brain states.

Disclosures: Y. Mu: None. **Z. Wei:** None. **D.V. Bennett:** None. **M. Rubinov:** None. **S. Narayan:** None. **C. Yang:** None. **M. Tanimoto:** None. **B.D. Mensh:** None. **L. Looger:** None. **M.B. Ahrens:** None.

Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.03

Topic: B.11. Glial Mechanisms

Support: Independent Research Fund Denmark
Lundbeck Foundation
Augustinus Foundation

Title: Disconnection between arousing input and astrocytes during sleep

Authors: *C. KJAERBY[1], M. ANDERSEN[1], H. HIRASE[1], M. NEDERGAARD[2,1];
[1]Ctr. for Translational Neuromedicine, Univ. of Copenhagen, Copenhagen, Denmark;
[2]Neurosurg. Ctr. Aging & Devel Biol, Univ. of Rochester, Rochester, NY

Abstract: Astrocytes are glial cells with an abundant brain-wide distribution, and recent evidence suggests that they play a role in promoting the transition between awake and sleep state through regulation of the extracellular ion environment. During awake behavior, astrocytes display intracellular calcium increases in response to noradrenaline released by activation of the arousal center of brain, locus coeruleus (LC). LC is a brain stem nucleus involved in the promotion of wakefulness and is integrally involved in regulation of sleep and wake transitions. We wanted to determine whether the coupling between LC and astrocytic calcium activation was changed during sleep conditions. We used *in vivo* calcium imaging of LC noradrenergic neurons and prefrontal astrocytes to determine the activity pattern of these two cell populations in mice experiencing naturally occurring sleep and wake episodes. We discovered that during sleep, LC displayed distinct high-amplitude phasic firing and that the LC-astrocytic relationship was disconnected compared to awake states. We speculate that this decoupling is needed in order to promote an external environment promoting sleep.

Disclosures: C. Kjaerby: None. **M. Nedergaard:** None. **M. Andersen:** None. **H. Hirase:** None.

Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.04

Topic: B.11. Glial Mechanisms

Support: IRP of NINDS

Title: Astrocytes regulate brainstem respiratory rhythm-generating circuits

Authors: *S. SHEIKHBAHAEI[1], H. KOIZUMI[1], R. ZHANG[1], A. V. GOURINE[2], J. C. SMITH[1];
[1]Cell. and Systems Neurobio. Section, NIH, Bethesda, MD; [2]Univ. Col. London, London, United Kingdom

Abstract: Astrocytes, the electrically silent CNS cells, have been proposed to modulate neuronal network activity, including vital brainstem respiratory rhythm-generating circuits of the preBötzinger complex (preBötC), although such a modulatory function at the level of preBötC circuits has not been directly demonstrated. Previously, in conscious adult rats and using viral vector technologies, we have shown that interfering with vesicular release mechanisms of preBötC astrocytes significantly reduced the resting respiratory rate and frequency of periodic sighs, decreased rhythm variability, impairs respiratory responses to hypoxia and hypercapnia, and dramatically reduces the exercise capacity. Here, to identify the signaling molecules from astrocytes to neurons, we employed transgenic mice expressing Cre recombinase under control of the human glial fibrillary acidic protein (hGFAP-cre) promoter for astrocyte-specific expression of Channelrhodopsin-2 (ChR2) or archaerhodopsin (Arch) and applied optogenetic techniques to manipulate preBötC astrocytes in rhythmically active medullary slices *in vitro*. Activation of Arch in preBötC astrocytes via laser (593 nm, 2-10 mW) decreased the frequency and amplitude, and eventually eliminated, of hypoglossal nerve (XII) activity in hGFAP-Arch mice (n=5), whereas photoactivation of ChR2 (473 nm, 0.5-5 mW) in preBötC astrocytes increased the frequency of XII activity in hGFAP-ChR2 mice in a laser-power dependent manner (up to 110% increase at 5 mW). The laser-induced increase in XII frequency was not affected by blocking purinergic (ATP/adenosine) signaling (MRS2179, 100 uM, n=3; DPCPX, 1 uM, n=3), but was attenuated by ~50% when L-lactate (LL) was inhibited with a competitive inhibitor (D-lactate, 10 mM, n=4). A similar effect was observed when LL synthesis was blocked with the glycogenolysis inhibitor DAB (n=3). The effect of DAB was rescued by bath application of LL (4mM; n=3). Moreover, inhibition of LL transporters (by 4-CIN, 250 uM, n=3) decreased laser-induced XII activity by ~50%. In the CNS, only astrocytes can store glycogen, convert it to LL, and release LL. Our results suggest that LL released from optogenetically-stimulated astrocytes acts as a novel signaling molecule exciting preBötC circuits.

Disclosures: S. Sheikhbahaei: None. **H. Koizumi:** None. **R. Zhang:** None. **A.V. Gourine:** None. **J.C. Smith:** None.

Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.05

Topic: B.11. Glial Mechanisms

Support: Po1 HL126523
PO1 HL090554

Title: Neuroglial coupling underlies sigh rhythmogenesis in the preBötzinger complex

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Abstract: Sighs are large amplitude inspirations that occur periodically during normal breathing and are physiologically important for preventing alveolar collapse. Normal or “eupneic” inspirations and sighs originate from the same neuronal network, the preBötzinger Complex (preBötC), in the ventral medulla. Yet, it remains unknown how the same inspiratory network generates and coordinates these two distinct rhythmic activities. We developed an in-silico model of the preBötC network that generates both eupneic and sigh activities by incorporating a source of slow calcium oscillations. Based on our model, we hypothesized that preBötC astrocytes are the source of these oscillations and propose this external oscillator as the primary mechanism driving sigh rhythmogenesis. We tested this hypothesis by combining computational modelling with experimental approaches performed in rhythmic brainstem slices isolated from neonatal mice.
We found brainstem astrocytes that displayed an increase in intracellular calcium (fura-2) corresponding to sigh activity. Next, we proposed that purinergic receptor signaling contributes to this calcium change in astrocytes mediated by the release of ATP. Sighs were increased 2-fold by light uncaging of ATP *in vitro.* Furthermore, we found that sigh frequency could be enhanced by application of the purinergic P2Y1 receptor agonist and eliminated with the P2Y1R, but not P2XR, antagonist. Increases in sigh frequency by the Beta-adrenergic agonist isoproterenol were also blocked by the P2Y1 antagonist. We then used optogenetics in combination with extracellular population recordings to drive ChR2 expression under control of the astrocytic promoter Aldh1l1.
Sighs were elicited with light activation of Aldh1l1 expressing preBötC astrocytes and severely inhibited by applying P2Y1 blockade and low concentrations of the P/Q type Ca^{2+} channel blocker cadmium (4μM). Sighs under control conditions and with application of the muscarinic receptor agonist oxotremorine were elicited within the limits defined by the refractory period. Taken together, our experiments suggest that the timing characteristics underlying sigh generation are a coordinated action between glial calcium oscillations and the neural network dynamics that underly inspiratory behaviors.

Disclosures: L. Severs: None. **N.A. Baertsch:** None. **T.I. Dashevskiy:** None. **J. Ramirez:** None.

Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

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Topic: B.11. Glial Mechanisms

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NSF GRFP

Title: Astrocytes alter classic and non-canonical glutamate signaling in awake animal models of migraine

Authors: *P. D. PARKER[1], P. S. SURYAVANSHI[1], M. MELONE[2], K. M. REINHART[3], P. M. SAWANT[1], J. J. THERIOT[1], A. PUGLIESE[4], F. CONTI[4], C. W. SHUTTLEWORTH[3], D. PIETROBON[5], K. BRENNAN[6];
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Abstract: Astrocytes maintain the fidelity of excitatory synaptic signaling by limiting glutamate in the extracellular space. How impaired uptake reshapes glutamate signaling in a living animal under normal and disease conditions is less understood. Familial hemiplegic migraine type 2 (FHM2) is a monogenic subtype of migraine with aura due to loss-of-function mutations in the astrocytic α2 Na^+/K^+-ATPase. Knock-in (KI) mice carrying a human FHM2 mutation have a concomitant decrease in the glutamate transporter GLT-1a and slowed uptake of glutamate by cortical astrocytes. We recorded glutamate signaling in awake mice using a genetically encoded glutamate indicator (iGluSnFR) and confirmed slowed clearance rates following whisker stimulation in KI relative to wild-type (WT) littermates. Unexpectedly, we observed novel glutamatergic events (or plumes) that appeared to diffuse from a central source and were distinguishable from whisker mediated signaling. Mechanistically, astrocyte glutamate uptake efficiency appeared to influence plume occurrence. Plumes occurred frequently in KI, but rarely in WT; plumes correlated with decreased density and greater distance of GLT-1+ astrocyte processes from excitatory synapses in superficial cortical L1 vs L2/3; and pharmacological inhibition of glutamate transporters robustly induced plumes in *in vivo* and *in vitro* models, regardless of genotype. The source of glutamate, however, appeared neuronal, as plumes were Ca^{2+} dependent vesicular release. Blocking voltage gated sodium channels (VGSC) did not inhibit plumes, though decreasing VGSC inactivation increased the frequency of plumes, indicating a Ca^{2+} mediated mechanism downstream of action potentials may be important. Plumes may also have translational significance in migraine: plumes accompanied a rise in extracellular glutamate preceding experimentally induced cortical spreading depression (CSD; the physiological event that underlies migraine aura) at its ignition site. The rise in glutamate was steeper in KI vs WT, and KI had a lower CSD threshold, consistent with impaired glutamate

buffering, and a potential role for plumes, in CSD generation. Moreover, CSD itself induced plumes outside the ignition site. In summary, using a genetic model of migraine, we found impaired astrocytic uptake prolonged glutamate signaling during sensory processing, was associated with non-canonical glutamatergic plumes, and impaired glutamate buffering in a manner that may aid the generation of migraine relevant phenotypes. We present plumes as a product of neuroglial imbalance due to increased neuron glutamate release relative to astrocyte clearance capabilities.

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Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.07

Topic: B.11. Glial Mechanisms

Support: RFBR COMFI grant 17-00-00412 (K)
RFBR grant 17-00-00409
RFBR grant 17-00-00407
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Title: Spatiotemporal properties of calcium activity in single astrocytes and astrocytic networks

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Abstract: Astrocytes are electrically passive cells and use their transmembrane gradients for ionic signaling mediated by Na^+, K^+, and Ca^{2+}. Ca^{2+} imaging provides a convenient readout of astrocytic activity, which often takes form of spreading regenerative events. Ca^{2+} events predominantly nucleate in thin astrocytic processes and spread within individual cells and astrocytic networks. Commonly used region-of-interest (ROI)-based approach for analysis of astrocytic Ca^{2+} activity captures the complexity of Ca^{2+} signaling neither in individual astrocytes nor at the network level. We imaged Ca^{2+} activity in astrocytes expressing genetically encoded Ca^{2+} sensor GCaMP6 or loaded with membrane-permeable Ca^{2+} dye Oregon Green BAPTA-AM in mouse hippocampal slices. We identified individual Ca^{2+} events using matrix factorization techniques in small overlapping patches. The following parameters of Ca^{2+} events were obtained:

maximal projection (spread), duration, speed of expansion/contraction, rate of fluorescence increase/decrease. These parameters can be used to characterize complex mechanisms responsible for a wide repertoire of Ca^{2+} events in astrocytes: Ca^{2+} mobilization, intracellular spread, and clearance. Next, we analyzed the pattern of Ca^{2+} activity in the astrocytic network. We report fluctuations in the percentage of the active pixels and the number of Ca^{2+} event cross-sections in time. We are now analyzing changes in the described parameters in response to extracellular stimulation and pharmacological treatment of the slices. We monitor changes in astrocytic Ca^{2+} activity in an animal model of epilepsy and Alzheimer's disease.

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Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

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Presentation Number: 266.08

Topic: B.11. Glial Mechanisms

Support: Beckman Graduate Fellowship (GNK)
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Title: Diurnal morphological and coupling dynamics in hippocampal dentate gyrus astrocytes 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 previously have demonstrated a significant diurnal difference in astrocyte branching complexity in the hippocampal 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 the 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, enables imaging of substantially thicker specimens than previously achieved with standard fluorescence-labeling techniques. This is an add-on module to the electrophysiology rig that enables us to obtain dry mass values and cell volume measurements in addition to electrophysiological data that can then be used to quantify the difference in astrocyte branching complexity over the day-night cycle. Our results from whole-cell patch-clamp recording of astrocyte networks in 5 rats of 3-6 weeks of age per time point found distinct day-night coupling properties of hippocampal DG astrocyte populations. 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 low resistances at both time points. Additionally, our preliminary data from GLIM imaging in 10 animals per time point suggest that the hippocampal DG astrocytes display significantly greater volume and dry mass during nighttime, the active phase of the nocturnal animal. Measurements of dry mass and volume from tens to hundreds of astrocytes through fluorescence Z-stack imaging confirm and extend the finding of significant diurnal network dynamics obtained through our label-free imaging technique. 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.

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Nanosymposium

266. Astrocyte Networks Controlling Brain Function and Behavior

Location: Room S103

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 266.09

Topic: B.11. Glial Mechanisms

Title: Artificial astrocyte networks

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Abstract: Using a simple mixture of sigmoid tuning curves, Barron (1993) proved artificial neural networks are universal function approximators. Here we show that Barron's theoretical work extends to astrocyte networks, if we replace firing rate with calcium concentration. This is because 1) astrocytes release neurotransmitters based on the calcium level and 2) the calcium response to neurotransmitter detection is approximately sigmoidal. In practice, artificial astrocyte networks--with only nearest-neighbor connections--achieve good performance on a range of machine learning tasks, including classic MINST visual digit recognition. Our practical success using artificial astrocytes suggests the diffuse, non-synaptic, connectivity and slow calcium dynamics of biological glia don't fundamentally limit their computational capacity.

Disclosures: **E. Peterson:** None. **T.D. Verstynen:** None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.01

Topic: C.03. Parkinson's Disease

Support: Intramural funds to J.R. Leheste

Title: Bacterial Parkinson's disease: Findings, implications and treatment opportunities

Authors: ***J. R. LEHESTE**[1], C. A. BIEGEL[2], S. GOTTLIEB[2], K. KULASON[2], V. CIMINO[2], K. CHU[2], P. PRABHU[2], D. ORSHAN[2], G. OTAZU ALDANA[2];
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Abstract: After decades of research and billions of research dollars spent, effective preventative measures or a cure for Parkinson's disease (PD) are still elusive. Here, we are presenting findings generated *ex vivo* (*post-mortem* human brain tissue), *in vivo* (mice) and *in vitro* (human cells) supporting a bacterial infectious pathogenesis for PD. While the work in *post-mortem* human brain tissue is concentrated on bacterial distribution and immediate pathophysiological consequences, mechanisms and behavior are addressed in animal models supported by work in cultured human cells. The main research objective focuses on bacterial brain entry *via* the naso-olfactorial route. This aligns well with the early cellular and behavioral signs of PD, such as Lewy body pathology in the olfactory bulb and olfactory sensory reduction (hyposmia), respectively. Much of the work in tissues and cells is generated using classical histological and immuno-histochemical techniques. Mechanisms, triggered responses and identifications are predominantly assessed via protein- DNA- and RNA-based techniques (ELISA, PCR and qPCR, respectively). Behavioral measures are based on tests previously established for motor-behavior and olfaction. Our findings establish the naso-olfactorial route as a bacterial entry point to the brain. While control infections are efficiently cleared, even after bacterial brain entry, the skin acne-associated *Propionibacterium acnes* persists within neurons and interstitial biofilm. Our results recapitulate much of the consequences established for cells, tissues and behavior in PD, ranging from inflammation, alpha-synuclein accumulation and cell death to reduced olfactorial sensation and reduced motor function. Our next steps will focus on disease prevention and management with antibacterial agents and antibiotics.

Disclosures: **J.R. Leheste:** None. **C.A. Biegel:** None. **S. Gottlieb:** None. **K. Kulason:** None. **V. Cimino:** None. **K. Chu:** None. **P. Prabhu:** None. **D. Orshan:** None. **G. Otazu Aldana:** None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.02

Topic: C.03. Parkinson’s Disease

Support: ERC Advanced Grant 'Repropark' Ref:340527
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Department of Health, Government of Navarra Ref: 046-2017-NAB7
Ciberned Intramural Grant Ref: 2017/02

Title: Glucocerebrosidase gene therapy in a nonhuman primate model of Parkinson's disease

Authors: *J. L. LANCIEGO[1,3], A. J. RICO[1,3], D. MARIN-RAMOS[1], E. RODA[1,3], G. GONZALEZ-ASEGUINOLAZA[2], A. I. RODRIGUEZ[5,4], M. COLLANTES[6], I. PENUELAS[6], J. L. LABANDEIRA-GARCIA[5,4], D. SUCUNZA[1,3];
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Abstract: Mutations in the GBA1 gene coding for the lysosomal enzyme glucocerebrosidase (GCase) are related to increased incidence of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although the mechanisms trhough which GCase regulates the homeostasis of alpha-synuclein still are not fully understood, the identification of reduced GCase lysosomal activity as a common feature sustaining the neuropathological findings underlying PD and DLB -even when considering sporadic forms of these synucleinopathies- has recently attracted strong interest in the field. Accordingly, a number of novel strategies focused on increasing GCase activity to reduce alpha-synuclein burden and preventing dopaminergic neuronal death have been designed. Here we have performed bilateral injections of a recombinant adeno-associated viral vector serotype 9 coding for the mutated form of human alpha-synuclein (rAAV9-SynA53T) for disease modeling purposes in nonhuman primates (NHPs), further inducing a progressive neuronal death in the substantia nigra pars compacta (SNc). Next, another rAAV9 coding for the GBA1 gene (rAAV9-GBA1) was unilaterally delivered in the SNc of NHPs one month after initial insult with rAAV9-SynA53T, together with the contralateral delivery of an empty rAAV9 (rAAV9-null) for control purposes. Obtained results showed that rAAV-mediated enhancement of GCase activity reduced alpha-synuclein burden, leading to improved survival of dopaminergic neurons together with a reduction in microglial-driven pro-inflammatory phenomena. Furthermore, the trans-synaptic spread of mutated alpha-synuclein was impeded upon treatment with rAAV9-GBA1. Data reported here

support the use of glucocerebrosidase gene therapy as a disease-modifying treatment for PD and related synucleinopathies, also including sporadic forms of these disorders.

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Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.03

Topic: C.03. Parkinson's Disease

Title: Preclinical efficacy of the glucosylceramide synthase inhibitor Venglustat correlates with CSF and CNS exposure

Authors: C. VIEL, J. CLARKE, A. RICHARDS, H. PARK, B. WANG, L. GAO, L. S. SHIHABUDDIN, *S. SARDI;
Sanofi, Framingham, MA

Abstract: Mutations in *GBA*, the gene encoding the lysosomal enzyme glucocerebrosidase (GCase), represent the greatest genetic risk factor for developing synucleinopathies including Parkinson's disease (PD). Additionally, PD patients harboring a mutant *GBA* allele present with an earlier onset of disease and an increase in the progression and severity of both motor and non-motor symptoms. Preclinical studies in mouse models of synucleinopathies suggest that inhibition of glucosylceramide synthase (GSC) using a CNS-penetrant small molecule may be a potential treatment for synucleinopathies. We have previously shown that brain GSC inhibition reduced the accumulation of glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph), slowed the accumulation of alpha-synuclein hippocampal aggregates, and improved the associated cognitive deficits [Sardi et al., PNAS 2017]. Here, we studied the efficacy of a clinical candidate GCS inhibitor, venglustat, in a mouse model of *GBA*-related synucleinopathy ($Gba^{D409V/D409V}$). In addition, we validated GCS inhibition in the CNS as a therapeutic strategy for *GBA*-related PD by reducing endogenous GCS levels using an artificial micro-RNA (miRNA) approach. Lastly, we examined the pharmacokinetics of short-term GCS inhibition in the different bio-compartments including cerebrospinal fluid (CSF), plasma, and brain of $Gba^{D409V/D409V}$ mice to correlate drug exposure and GlcCer levels after treatment. GlcCer levels in CSF positively correlate with CNS GlcCer levels and may be used to confirm CNS target engagement. Collectively, these data further support the rationale for GCS inhibition as a therapeutic strategy for treating *GBA*-related synucleinopathies and the development of venglustat for *GBA*-related PD.

Disclosures: **C. Viel:** A. Employment/Salary (full or part-time):; Sanofi. **A. Richards:** A. Employment/Salary (full or part-time):; Sanofi. **H. Park:** A. Employment/Salary (full or part-time):; Sanofi. **B. Wang:** A. Employment/Salary (full or part-time):; Sanofi. **L. Gao:** A. Employment/Salary (full or part-time):; Sanofi. **L.S. Shihabuddin:** A. Employment/Salary (full or part-time):; Sanofi. **S. Sardi:** A. Employment/Salary (full or part-time):; Sanofi.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.04

Topic: C.03. Parkinson’s Disease

Title: Network centric therapy for deep brain stimulation status parametric analysis with machine learning classification

Authors: *R. C. L. LEMOYNE[1], T. J. MASTROIANNI[2], D. WHITING[3], N. TOMYCZ[3]; [1]Independent, Running Springs, CA; [2]Cognition Engin., Pittsburgh, PA; [3]Allegheny Hlth. Network, Pittsburgh, PA

Abstract: Network Centric Therapy enables the opportunity to interconnect the patient and clinical resources through wearable and wireless systems with Internet connectivity to Cloud computing resources. In particular, Network Centric Therapy offers considerable utility to the domain of movement disorders, such as Parkinson’s disease. The current state of the art for wearable and wireless systems has manifested with inertial sensor devices that have a profile on the order of a bandage. With this state of the art wearable and wireless system a parametric analysis of the available tuning configurations for deep brain stimulation regarding the treatment of Parkinson’s disease is conducted. Machine learning is applied to contrast the ascertained parameter configurations. The results demonstrate the successful ability to apply wearable and wireless systems from the perspective of Network Centric Therapy for the process of ascertaining deep brain stimulation system parameter configurations with machine learning classification. These findings further evolve the objective of achieving closed-loop optimization of deep brain stimulation system parameter configurations through extrinsic means.

Disclosures: **R.C.L. LeMoyne:** None. **T.J. Mastroianni:** None. **D. Whiting:** None. **N. Tomycz:** None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

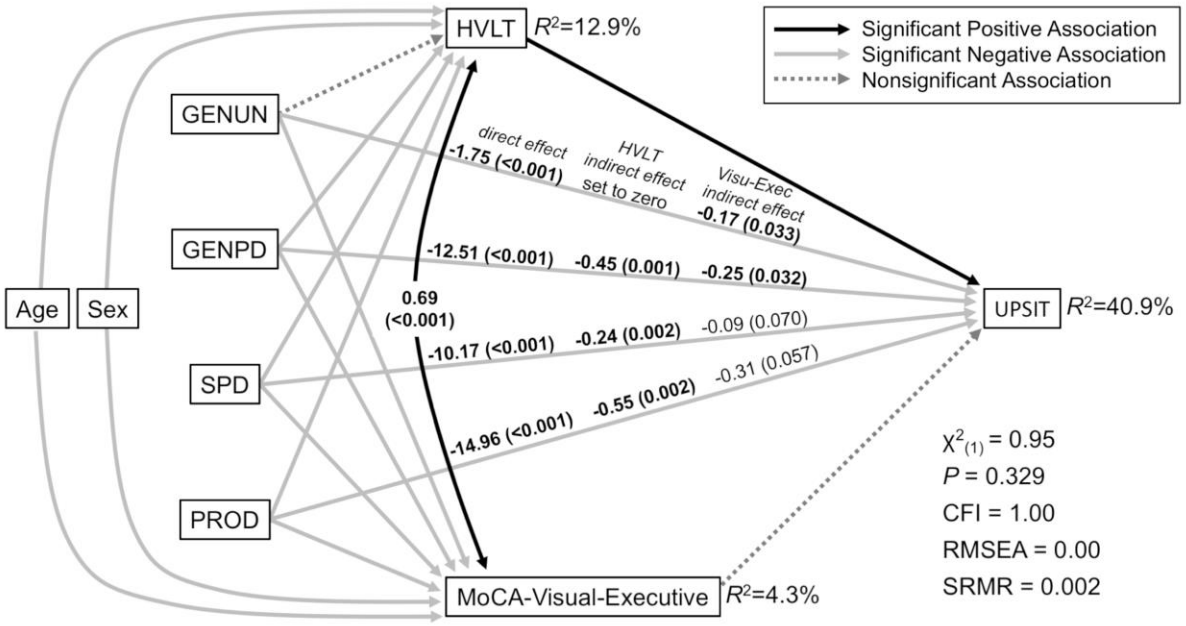
Presentation Number: 267.05

Topic: C.03. Parkinson's Disease

Title: Cognitive processes that indirectly affect olfactory dysfunction in Parkinson's disease

Authors: *A. T. MERTENS[1], J. B. SANTO[2], K. MARKOPOULOU[3], B. A. CHASE[4]; [1]Psychology, Univ. of Nebraska At Omaha, Omaha, NE; [2]Psychology, Univ. of Nebraska at Omaha, Omaha, NE; [3]Neurol., NorthShore Univ. HealthSystem, Glenview, IL; [4]Dept Biol, Univ. Nebraska-Omaha, Omaha, NE

Abstract: In Parkinson's disease (PD), olfactory dysfunction is a non-specific, non-motor symptom that often appears before motor-symptom onset. To understand how cognitive processes contribute to performance on the University of Pennsylvania Smell Identification Test (UPSIT), a clinically used test of olfactory function, we evaluated 1,280 subjects enrolled in the Parkinson's Progression Marker's Initiative (PPMI) across five diagnostic categories: sporadic PD (n=491), asymptomatic (n=310) and symptomatic (n=220) genetic PD, prodromal (n=61) and healthy controls (n=198). Structural equation modeling found that scores on tests of global cognition (Montreal Cognitive Assessment, MoCA), verbal learning and memory (Hopkins Verbal Learning Test, HVLT), and visuospatial/executive functioning (MoCA subscore) each explain some of the variance in UPSIT scores. When MoCA and HVLT scores are included in the same structural equation model, HVLT scores ($-0.53<b<-0.23$, $0.001<p<0.005$), but not MoCA scores, are significant in explaining performance on the UPSIT in the symptomatic diagnostic categories. When MoCA scores are replaced by MoCA subscores for visuospatial/executive function in this model, HVLT scores remain significant in explaining performance on the UPSIT for the symptomatic diagnostic categories ($-0.55<b<-0.24$, $0.001<p<0.002$) and the MoCA visuospatial/executive function subscores are significant in explaining performance on the UPSIT for both of the genetic-PD diagnostic categories ($-0.25<b<-0.17$, $0.032<p<0.033$) (Figure). Thus, impairment of cognitive processes involved in verbal learning and memory and visuospatial/executive function contributes to lower UPSIT performance in PD diagnostic categories. These findings provide novel insights into mechanisms underlying olfactory dysfunction in PD.



Disclosures: **A.T. Mertens:** A. Employment/Salary (full or part-time):; University of Nebraska at Omaha. **J.B. Santo:** A. Employment/Salary (full or part-time):; University of Nebraska at Omaha. **K. Markopoulou:** A. Employment/Salary (full or part-time):; Northshore University HealthSystem, University of Chicago Pritzker School of Medicine. **B.A. Chase:** A. Employment/Salary (full or part-time):; University of Nebraska at Omaha.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

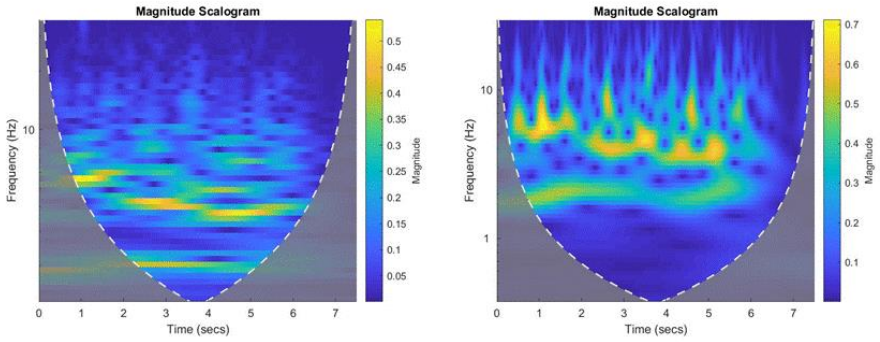
Presentation Number: 267.06

Topic: C.03. Parkinson’s Disease

Title: Wavelet shapes for feature extraction in accelerometry in Parkinson’s disease

Authors: *T. H. HARRIGAN[1], J. R. BRASIC[2], K. A. MILLS[3], B. J. HWANG[4], C. MISHRA[5], A. PANTELYAT[6], P. VYAS[7], D. F. WONG[8];
[1]Johns Hopkins Univ. Applied Physics Laborator, Baltimore, MD; [2]The Russell H. Morgan Dept. of Radiology and Radiological Sci., Johns Hopkins Sch. of Med., Baltimore, MD; [3]Neurol., [4]Neurosci., Johns Hopkins Univ., Baltimore, MD; [5]JOHNS HOPKINS SCHOOL OF MEDICINE, Baltimore, MD; [6]Neurol., [7]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [8]Radiology, Johns Hopkins Med. Insts., Baltimore, MD

Abstract: Clinical grading of the changes in movement in Parkinson's disease and similar disorders is based on several factors, including tremor, slowness, and features such as halting. Accelerometry offers the chance to standardize observations or to provide data for remote diagnosis. The purpose of this study is to assess how well acceleration histories can be used to standardize or augment clinical observations**. Methods:** In this study 20 patients with Parkinson's disease were instrumented with tri-axial accelerometers on the upper and lower extremities during 12 modified segments of the of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, *et al.* , 2008; McKay GN, Harrigan TP, Brasic JR. A low-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's disease. MethodsX 2019; 6: 169-189. https://doi.org/10.1016/j.mex.2018.12.017). Accelerometers were attached bilaterally to the forearm and index finger for upper extremity tests, and to the great toe and tibia for lower extremity tests. The acceleration data was analyzed using several wavelet transform types, to assess how well the shapes can detect halting or slowing. The results of the transforms were correlated to the clinical observations. **Results:** Figure 1 shows typical results in a 76 year old patient with mild impairment the upper extremity finger tapping test. Morlet waveform detects transients better than the bump waveform on MATLAB. **Conclusions:** The Morlet wavelet components reflect clinical observations and provide data to quantify measures such as rhythm, slowing, and interruptions. This procedure can show subtleties that are not perceived by clinical examination. will likely facilitate obtaining objective data to monitor movements in people with Parkinson's disease during clinical trials and other interventions, and it can clarify the specific components of movement that influence a clinical assessment.



Disclosures: T.H. Harrigan: None. **J.R. Brasic:** None. **K.A. Mills:** None. **B.J. Hwang:** None. **C. Mishra:** None. **A. Pantelyat:** None. **P. Vyas:** None. **D.F. Wong:** None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.07

Topic: C.03. Parkinson’s Disease

Support: EC grant 769574-HOLOBALANCE

Title: Which Parkinson's disease motor deficits are ameliorated by STN stimulation

Authors: *C. F. MAURER;
Neurol., Albert Ludwigs Univ., Freiburg, Germany

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves motor deficits caused by Parkinson's disease (PD). Some motor deficits respond better to STN stimulation and some less, as e.g. postural control or axial deficits. Whether this heterogeneous effect of STN stimulation could be assigned to certain motor tasks, motor features (e.g. movement amplitude, speed, variability, smoothness, intersegmental coordination), or body segments is not known yet. Here, we aim to identify the quality and the quantity of STN stimulation effects on PD motor symptoms, depending on stimulation parameters such as amplitude, and the stimulation pulse profile. We applied motion capture techniques to monitor motor behavior across different motor tasks in 20 PD patients with STN stimulation switched off and on, and in 25 healthy control subjects. Displacement- and velocity-related motor effects of STN stimulation are superior to effects related to the smoothness of motor behavior. The distribution of STN stimulation effects across body segments is related to specific combinations of motor tasks and motor features. For example, the STN stimulation effect on trunk velocity is significant in a sit-to-stand task and negligible in ‘functional reach’ movements. We conclude that the effect of STN stimulation varies as a function of motor task, and motor feature, which then determines the distribution of the effect across body segments. Motor features related to smoothness are less affected, compared to displacements and velocities of movements. This new motion analysis approach may allow for a better titration of therapeutic interventions in future, such as the potentially continuous adjustment of STN stimulation parameters, depending on motor tasks and desired type of amelioration of motor performance.

Disclosures: C.F. Maurer: None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.08

Topic: C.03. Parkinson's Disease

Title: Frontal cortex of living patients with Parkinson's disease exhibits altered mRNA splicing profile

Authors: *S. M. BENOIT[1], H. XU[1], S. SCHMID[2], M. O. HEBB[1];
[1]Clin. Neurolog. Sci., [2]Anat. and Cell Biol., Western Univ., London, ON, Canada

Abstract: Introduction: Alternative mRNA splicing (AS) is an important biological mechanism which occurs in greater than 90% of protein coding genes allowing generation of multiple functional proteins from a single gene. Mounting evidence suggests that AS aberrations, particularly those caused by mutations, lead to the development of cancers, muscular dystrophy and neurodegenerative diseases. In Parkinson's disease (PD), specific alternatively spliced isoforms of alpha-synuclein mRNA show an increased propensity for aggregation suggesting a role for AS in the disease. RNAseq can better detect mRNA splicing events compared to previous technologies, but has only been reported in PD using peripheral or cadaveric tissues. While informative, these studies cannot provide the sensitivity and specificity needed to accurately study highly dynamic AS. **Hypothesis and Objective:** Small-volume cortical biopsies from living PD patients obtained during surgery for implantation of deep-brain stimulation electrodes may offer a novel, safe and highly sensitive tissue source to identify CNS-relevant AS aberrations. This pilot study sought to determine feasibility and compare AS profiles in cortical samples from PD and control patient cohorts using RNA-seq. **Methods:** Total RNA was extracted from fresh cortical biopsies (6 PD, 5 controls) and sequenced on an Illumina HiSeq 2500 unit. Analysis to identify differential alternative splicing was performed with Spliceseq (v.2.10) and 6 selected events were validated using quantitative real-time PCR. **Results:** Sequencing using a paired-end protocol generated approximately 90 million 125 base pair length reads per sample. 646 AS events were identified as significantly altered in PD samples compared to controls. There was broad transcriptome representation with notable foci of significance in genes responsible for regulating AS, including 31 zinc-finger proteins, spliceosome components SRSF1 and 2; and CDC-like kinases 1, 3, and 4. Splicing of key regulator of differentiation and proliferation FOS was also altered significantly. **Conclusions:** Access to living brain tissue for research on PD is exceptional and represents an important opportunity to improve our understanding of disease pathophysiology. This first demonstration of differential AS in cortical samples from living PD patients using our novel approach offers new insights with the potential to uncover a unique gene expression signature specific to PD, key to giving rise to precise clinical assays. Further research may well lead to the development of disease-modifying therapies for this devastating neurodegenerative disease.

Disclosures: S.M. Benoit: None. **H. Xu:** None. **S. Schmid:** None. **M.O. Hebb:** None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.09

Topic: C.03. Parkinson's Disease

Title: Test-retest of a coding form for a low-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's disease

Authors: *J. R. BRASIC[1], T. HARRIGAN[3], B. J. HWANG[4], A. K. MATHUR[1], K. A. MILLS[2], A. PANTELYAT[2], J. BANG[2], L. ROSENTHAL[2], E. MOUKHEIBER[2], K. KITZMILLER[1], J. M. ROBERTS[1], P. VYAS[1], A. B. SYED[1], D. F. WONG[1];
[1]The Russell H. Morgan Dept. of Radiology and Radiological Sci., [2]Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]REDD, Johns Hopkins Univ. Applied Physics Laborator, Laurel, MD; [4]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Objective: To assess the feasibility of a test-retest procedure for a coding form (Goetz CG, *et al.* Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement Disorders 2008; 23: 2129-2170; McKay GN, Harrigan TP, Brasic JR. A low-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's disease. MethodsX 2019; 6: 169-189. https://doi.org/10.1016/j.mex.2018.12.017). **Methods:** Ten participants with Parkinson's disease (PD) and four healthy control (HC) participants were assessed with the above protocol. **Results:** Ten participants (8 men, 2 women) with PD aged 45 to 83 (mean 63.78 $\pm$ 11.62) underwent a test of the above protocol and a retest one to 33 months (mean 11.67 $\pm$ 10.27), and four age- and sex-matched HC participants aged 55 to 73 (mean 64 $\pm$ 8.83) underwent a test and a retest 1 to 3 months (mean 2.00 $\pm$ 0.82) later. Scores of the test procedure were subtracted from retest scores. Age in years at first testing and the months between testing were recorded. The use of and response to levodopa and deep brain stimulation for each session were recorded. The table summarizes the results of the items. **Conclusions:** Scores at test and retest varied little for most items. The one patient who underwent the insertion of deep brain stimulation between sessions showed dramatic improvement. The use of this protocol for people with PD of all degrees of severity is feasible. Test-retest reliability will be assessed with larger samples. The protocol including the use of instrumentation to record quantitative continuous movement measurements along with clinical ratings of key tasks to identify problems of people with PD offers great promise to provide a higher level of accuracy and precision for the assessment of individuals with PD, atypical parkinsonism, and related conditions. Clinical implementation of this method may also assist clinicians in differentiating between various movement disorders, potentially allowing for earlier disease-specific therapies. It also has significant potential for at-home use in telemedicine applications.

Test-retest of a low-cost quantitative continuous measurement of movements in the extremities

	Sex:	Age	Month	3.17	3.17	3.15	3.15 Post	3.4 Fi	3.4 Fi	3.5 Han	3.5 Han	3.6 Pron	3.6 Pron	3.17	3.17	3.7 To	3.7 To	3.8	3.8

	Female = 0, Male = 1	in years	s between test and retest	Counting rest tremor amplitude upper limb right	Counting rest tremor amplitude upper limb left	Postural tremor of the hands right	ural tremor of the hands left	nger tapping right	nger tapping left	d movements right	d movements left	ation-supination movements of hands right	ation-supination movements of hands left	Counting rest tremor amplitude lower limb right	Counting rest tremor amplitude lower limb left	e tapping right	e tapping left	Leg agility right	Leg agility left
PD	1	57	33	-3	-4	-3	0	0	1	1	1	0	1	-3	-2	1	1	-1	0
PD	1	45	11	0	0	1	0	0	0	0	0	1	0	0	0	1	1	0	1
PD	0	62	5	0	-1	0	-2	-1	1	0	1	0	0	1	0	-1	0	0	0
PD	1	83	1	0	0	0	0	0	0	-1	-1	0	0	0	0	0	0	0	0
PD	1	60	3	0	1	1	-1	0	0	1	0	0	2	1	1	2	1	0	0
PD	1	67	18	-1	-1	-1	1	-3	-4	-1	-2	-1	0	0	0	-1	-1	1	1
PD	1	70	20	0	0	0	1	-1	-1	.	.	.	.	.	.	.	.	.	.
PD	1	76	6	0	1	0	0	-2	-1	2	1	1	1	0	1	-1	0	-1	0
PD	1	54	8	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
PD	0	72	5	0	0	0	0	1	1	0	2	-1	1	1	0	0	2	0	2
Number	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9
Mean	0.889	63.778	11.667	-0.444	-0444	-0.222	-0.111	-0.777	-0.444	0.25	0.125	0.125	05	-0.125	0.125	0.125	0.25	-0.125	0.25
Standard deviation	0.333	11.617	10.271	1.013	1.509	1.201	0927	1.092	1.509	1.035	1.125	0.640	0.755	1.246	0.991	1.125	0.707	0.640	0.462
HC	1	70	2	0	0	0	0	0	1	-1	0	0	0	0	0	0	1	0	1
HC	1	58	2	1	0	1	0	0	0	1	1	1	1	0	0	-1	0	1	1
HC	1	55	3	0	0	1	-1	1	-1	-1	-1	-1	0	0	0	0	0	0	-1

HC	1	73	1	0	0	1	0	0	0	-1	0	0	0	0	0	0	0	0	1
Mean	1	64	2.000	0.25	0	0.75	-0.25	0.25	0	-0.5	0	0	0.25	0	0	-0.25	0.25	0.25	0.5
Standard deviation	0	8.831	0.816	0.5	0	0.5	0.5	0.5	0.816	1	0.816	0.816	0.5	0	0	0.5	0.5	0.5	1
Differences of scores (retest-test) for participants Parkinson's disease (PD), healthy controls (HC)																			

Disclosures: **J.R. Brasic:** None. **T. Harrigan:** None. **B.J. Hwang:** None. **A.K. Mathur:** None. **K.A. Mills:** None. **A. Pantelyat:** None. **J. Bang:** None. **L. Rosenthal:** None. **E. Moukheiber:** None. **K. Kitzmiller:** None. **J.M. Roberts:** None. **P. Vyas:** None. **A.B. Syed:** None. **D.F. Wong:** None.

Nanosymposium

267. Parkinson's Disease: From Preclinical to Human Studies

Location: Room N426

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 267.10

Topic: C.03. Parkinson’s Disease

Support: NIH Grant ES024745
Michael J. Fox Foundation Grant

Title: Characterizing plasma-borne inflammasome-related proteins in Parkinson’s disease

Authors: *F. L. ANDERSON[1], K. M. VON HERRMANN[1], A. S. ANDREW[2], M. LEE[1], F. P. BISPO[4], A. L. YOUNG[1], W. F. HICKEY[3], M. C. HAVRDA[1];
[1]Dept. of Mol. and Systems Biol., [2]Dept. of Neurol., [3]Dept. of Pathology, Geisel Sch. of Med. at Dartmouth Col., Hanover, NH; [4]Dept. of Biol., St. Anselm Col., Manchester, NH

Abstract: Parkinson’s disease (PD) is a highly prevalent neurodegenerative disease characterized by loss of dopamine (DA) neurons within the substantia nigra pars compacta associated with severe motor impairments. Neuroinflammation is a widely-recognized aspect of PD pathophysiology however, the mechanisms of PD-related inflammation are not completely characterized. Inflammasomes, pro-inflammatory intracellular protein complexes containing pattern recognition receptors capable of initiating inflammation, have been associated with

neurodegenerative disease pathology, including that of Alzheimer's disease and more recently of PD. The NLRP3 inflammasome is of great interest due to its ability to respond to sterile triggers, such as misfolded proteins and reactive oxygen species, common in the brains of PD patients. Our studies have shown that: (1) the NLRP3 inflammasome is active in PD; (2) a polymorphism in *NLRP3* is associated with a reduced risk of PD; and (3) that inactivation of *Nlrp3* is neuroprotective in a mouse model of PD. NLRP3 activation can propagate a subcategory of pro-inflammatory programmed cell death called pyroptosis, a process characterized by cytoplasmic membrane pore formation and vesicular shedding. Based on the recognition that the NLRP3 inflammasome is activated in PD, and evidence that cytosolic proteins are released during pyroptosis, our lab tested the prediction that inflammasome-related proteins would be detectable in plasma obtained from PD patients. Using novel electrochemiluminescence-based assays, we identified NLRP3 and GSDMD proteins in human plasma samples collected from PD patients and aged-matched controls. Plasma NLRP3 levels were associated with PD and interrogation of survey data collected in our study identified NSAID use as negatively associated with NLRP3 levels. Seeking a cell-of-origin, we confirmed NLRP3 expression in peripheral blood mononuclear cells (PBMCs) in a subset of patients using real-time PCR and conducted single-cell sequencing analysis finding monocytes to be the primary cell type expressing inflammasome-related proteins in the periphery. Deeper characterization of the plasma-derived extracellular vesicles (EVs) containing inflammasome-related proteins showed evidence of neural origins, which corresponds with our finding of elevated inflammasome-related proteins in the brains of both PD patients and pre-symptomatic patients identified post-mortem as having mesencephalic cell loss. Overall, our findings suggest plasma-borne NLRP3 as a novel biologic indicator of systemic inflammation in PD and provide a useful tool for evaluating inflammasome activity in living patients.

Disclosures: **F.L. Anderson:** None. **K.M. von Herrmann:** None. **A.S. Andrew:** None. **M. Lee:** None. **F.P. Bispo:** None. **A.L. Young:** None. **W.F. Hickey:** None. **M.C. Havrda:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.01

Topic: D.07. Vision

Support: University of California Berkeley
Helen Wills Neuroscience Institute
NIH Grant F31EY027201
National Natural Science Foundation of China 31771251

Title: Human visual cortex is organized along two genetically opposed gradients with unique developmental and evolutionary origins

Authors: *J. GOMEZ[1], Z. ZHEN[2], K. S. WEINER[1];
[1]Psychology, Univ. of California Berkeley, Berkeley, CA; [2]Beijing Normal Univ., Beijing, China

Abstract: Human visual cortex is organized with striking consistency across individuals. While recent findings demonstrate an unexpected coupling between functional and cytoarchitectonic regions relative to the folding of human visual cortex, a unifying principle linking these anatomical and functional features of cortex remains elusive. To fill this gap in knowledge, we combined independent and ground truth measurements of cytoarchitectonic regions and genetic tissue characterization within human occipito-temporal cortex. Using a data-driven approach, we examined if differential gene expression among cytoarchitectonic areas could contribute to the arealization of occipito-temporal cortex into a hierarchy based on transcriptomics. This approach revealed two opposing gene expression gradients in human occipito-temporal cortex: one that contains a series of genes with expression magnitudes that ascend from posterior (e.g. areas hOc1, hOc2, hOc3, etc.) to anterior cytoarchitectonic areas (e.g. areas FG1-FG4) and another that contains a separate series of genes that show a descending gradient from posterior to anterior areas. Using data from the living human brain, we show that each of these gradients correlates strongly with variations in measures related to either thickness or myelination of cortex, respectively. We further reveal that these genetic gradients emerge along unique trajectories in human development: the ascending gradient is present at 10-12 gestational weeks, while the descending gradient emerges later (19-24 gestational weeks). Interestingly, it is not until early childhood (before 5 years of age) that the two expression gradients achieve their adult-like mean expression values. Additional analyses in non-human primates (NHP) reveal that homologous genes do not generate the same ascending and descending expression gradients as in humans. We discuss these findings relative to previously proposed hierarchies based on functional and cytoarchitectonic features of visual cortex. Altogether, these findings bridge macroscopic features of human cytoarchitectonic areas in visual cortex with microscopic features of cellular organization and genetic expression, which despite the complexity of this multi-scale correspondence, can be described by a sparse subset (~200) of genes. These findings help pinpoint the genes contributing to healthy cortical development, explicate the cortical biology distinguishing humans from other primates, as well as establish essential groundwork for understanding future work linking genetic mutations with the function and development of human visual cortex.

Disclosures: J. Gomez: None. **Z. Zhen:** None. **K.S. Weiner:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.02

Topic: D.07. Vision

Support: NIH Grant EY027018

Title: Typical functional selectivity and connectivity in category-selective visual cortex in children with unilateral ventral cortex resection

Authors: *M. BEHRMANN[1], S. KASTNER[2], M. A. PINSK[2], E. FREUD[3];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [3]Psychology, York Univ., Toronto, AB, Canada

Abstract: Surgical resection of the cortical epileptogenic zone is a successful procedure for seizure reduction in the treatment of pharmacologically intractable epilepsy. Many studies have noted that cognitive functions undergo surprising post-resection improvement, especially when surgery is undertaken earlier in life. Despite the key role that vision plays in human behavior, rather few studies have explored the functional outcomes following resection of visual cortex in children, who have the most potential for recovery. We have shown that, while hemianopia persists and retinotopic mapping does not become reorganized post-surgery, the behavioral profile of intermediate and high-level vision is within normal limits except in patients with significant comorbidities. The central question addressed here is what mechanism gives rise to the competence in those individuals with normal perceptual profiles. One hypothesis is that there is compensation or reorganization in the functional or effective connectivity between category-selective regions in the contralesional (preserved) hemisphere and perhaps even in the residual tissue in the ipsilesional hemisphere. This hypothesis was tested using data from five children who had undergone lobectomy surgery. Based on BOLD data from a functional localizer, including images of faces, buildings, words, common objects and scrambled patterns, we identified (in native space) all category-selective regions possible. We also demarcated the lateral geniculate nucleus and the pulvinar anatomically, given existing claims that subcortical regions may facilitate and regulate communication between cortical areas. Although widespread increases in connectivity were noted in one case with comorbidity (polymicrogyria), in the other cases, irrespective of side or site of resection, we documented entirely typical category-selective activation and functional connectivity between cortical-cortical and cortical-subcortical regions. These findings indicate that the good functional outcome is not obviously a consequence of rearranged functional networks and that alternative explanations ought to be sought.

Disclosures: M. Behrmann: None. **S. Kastner:** None. **M.A. Pinsk:** None. **E. Freud:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.03

Topic: D.07. Vision

Title: Discrete size tuning in the cortical receptive field mappings of Hubel & Wiesel

Authors: *C. W. TYLER;
Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Introduction. Two key issues in the cortical mapping of receptive field (RF) size are its population composition and its scaling with level in the visual hierarchy. Although it is well-established neurophysiologically that RF size spans only about a factor of 4 at any particular eccentricity (e.g. Gattass, Sousa & Rosa, 1987, J Comp Neurol), most computational models of visual processing operate on the assumption that there are channels of all sizes throughout the visual field. Conversely, in human vision, both electrophysiological (Tyler & Apkarian, 1981, New York Acad Sci) and psychophysical (Kontsevich & Tyler, 2015, J Vision) evidence suggests that there are two subpopulations of RF sizes in each local region of cortex, separated by about a factor of 3 in size (e.g., peaking at 3 arcmin and 9 arcmin in the fovea), with the sizes scaling with eccentricity.
Methods. An analysis of extrastriate receptive field (RF) data in macaque areas V2, V3 and V3A published posthumously in Hubel et al. (2013, Cereb Cortex), together with the original publication of V1 RF data (Hubel & Wiesel, 1974, J Comp Neurol), prompted a reanalysis of the RF sizes in the cortical (eccentricity-scaled) coordinate frame for the present study of RF size as a function of eccentricity and level in the cortical visual hierarchy.
Results. The distribution of eccentricity-scaled RF sizes was significantly bimodal in each cortical area, fitting a model of two discrete populations of RF sizes separated by about a factor of three. The size ranges for both sub-populations increased by about a log unit from V1 to V3A (reaching sizes of roughly 0.5 and 1.5 deg in foveal V3A, for example).
Conclusion. Thus, the reanalysis of these data pose a challenge to neural and computational models of extended object processing beyond their respective discrete sizes, implying that the local processing of spatial structure derives from the comparison of only two size signals, and that the mechanism for processing elongated or large stimuli in central vision must be deferred to the later stages of the visual hierarchy.

Disclosures: C.W. Tyler: None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.04

Topic: D.07. Vision

Support: NWO-STW P15-42 "NESTOR"
NWO-VENI 451-13-023

Title: Benchmarking population receptive fields with fMRI and large-scale neurophysiological recordings in awake non-human primates

Authors: *P. C. KLINK[1,2], X. CHEN[1], W. VANDUFFEL[3,4], D. DENYS[2,1], P. R. ROELFSEMA[1,2,5];
[1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Amsterdam UMC, Univ. of Amsterdam, Amsterdam, Netherlands; [3]KU Leuven, Leuven, Belgium; [4]Harvard Med. Sch., Boston, MA; [5]VU Univ., Amsterdam, Netherlands

Abstract: Population receptive field (pRF) mapping has become a popular method to quantitatively estimate the retinotopic organization of the human brain with fMRI. The method uses a forward model to fit receptive field properties to the BOLD signal under the assumption that this hemodynamic signal reflects the cumulative neuronal receptive field properties of large populations of neurons within an imaging voxel. While human population receptive field maps measured with fMRI are qualitatively similar to classic single-cell receptive fields derived from invasive neurophysiological recordings in animals, it remains unclear whether any differences are due to differences between species or a discrepancy between the BOLD signal and the underlying neuronal activity. As a consequence, it remains unclear what neuronal activity aspect is best captured by the tuning of the BOLD signal. We tackled this issue with an extensive within-species comparison of pRFs that were independently fit to either the BOLD signal or to different aspects of neuronal activity. To this end, we performed whole-brain fMRI in two awake non-human primates (*Macaca mulatta*) and large-scale neurophysiological recordings in V1 and V4 in two other animals, each implanted with chronic electrode arrays adding up to 1,024 electrodes per animal. For each of these electrodes, we independently fit pRFs to the multi-unit spiking activity (MUA) and local field potential (LFP) fluctuations in the theta (4-8 Hz), alpha (8-16 Hz), beta (16-30 Hz), low-gamma (30-60 Hz), and high-gamma (60-120 Hz) frequency ranges. Our fMRI data reproduced the well-known positive correlation between pRF-size and visual eccentricity, with steeper slopes in areas that are considered to be higher in the visual cortical hierarchy. A similar pattern was present in the neurophysiological data for V1 and V4, where pRFs could be well-characterized from the MUA and the gamma-components of the LFP in a large number of electrodes (>1,500 across two animals). In fewer electrodes, it was also possible to estimate pRFs from the lower frequency LFP components, with fits based on the alpha-power potentially providing information about the center-surround organization of the underlying neuronal populations. Finally, a cross-modal correlation analysis of pRF-maps indicated that the fMRI-based maps were most strongly correlated with neurophysiological maps based on the MUA and high-gamma LFP. These results suggest that BOLD-based pRFs, as measured with fMRI, mostly reflect the spiking activity of a relatively large population of neurons.

Disclosures: P.C. Klink: None. **X. Chen:** None. **W. Vanduffel:** None. **D. Denys:** None. **P.R. Roelfsema:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.05

Topic: D.07. Vision

Support: Marie Sklodowska-Curie grant agreement No. 661883

Title: Assessing uncertainty in cortico-cortical population receptive field estimations

Authors: *A. INVERNIZZI[1], K. V. HAAK[2], J. CARVALHO[1], R. J. RENKEN[1], F. W. CORNELISSEN[1];
[1]UMCG, Groningen, Netherlands; [2]Donders Ctr. for Cognitive Neuroimaging, Radboud Univ., Nijmegen, Netherlands

Abstract: The majority of neurons in the human brain process signals from neurons elsewhere in the brain. Therefore, it is critical to have methods that can describe this aspect of the brain's circuitry. Connective Field (CF) modeling (Haak et al., 2013) allows characterizing the response of a population of neurons in one part of the brain in terms of the activity in another part of the brain. It translates the concept of the receptive field into the domain of cortical connectivity by assessing the spatial dependency between signals in distinct cortical visual field areas. The standard CF method does not easily allow estimating parameter uncertainty. This somewhat limits its applicability, in particular for comparing alternative connective field models and studying connective plasticity in both healthy observers and patients with neuro-ophthalmic disease.Here, we present a novel Bayesian framework for the CF model to estimate the underlying distribution and uncertainty associated with each of the CF parameters (Figure 1). We validate our approach by comparing its performance to the standard CF using stimulus-driven (SD) and resting-state (RS) functional magnetic resonance imaging (fMRI) data at 3T, obtained in 12 observers. Next, we apply our new approach to compare CF models of different complexity (single vs. difference of Gaussians). Our results show a good level of agreement between both standard and Bayesian CF models for each CF parameter. Furthermore, we find that single gaussian (SG) models outperform models that assume a difference of gaussians (DoG) for both SD and RS data, and throughout the visual cortex. Hence, we conclude that our novel Bayesian framework can estimate and provide a measure of uncertainty for the estimated CF parameters. Moreover, the SG CF model is sufficiently able to capture fMRI negative signals indicating that the CFs of healthy observers are best modelled as centers without surrounds.

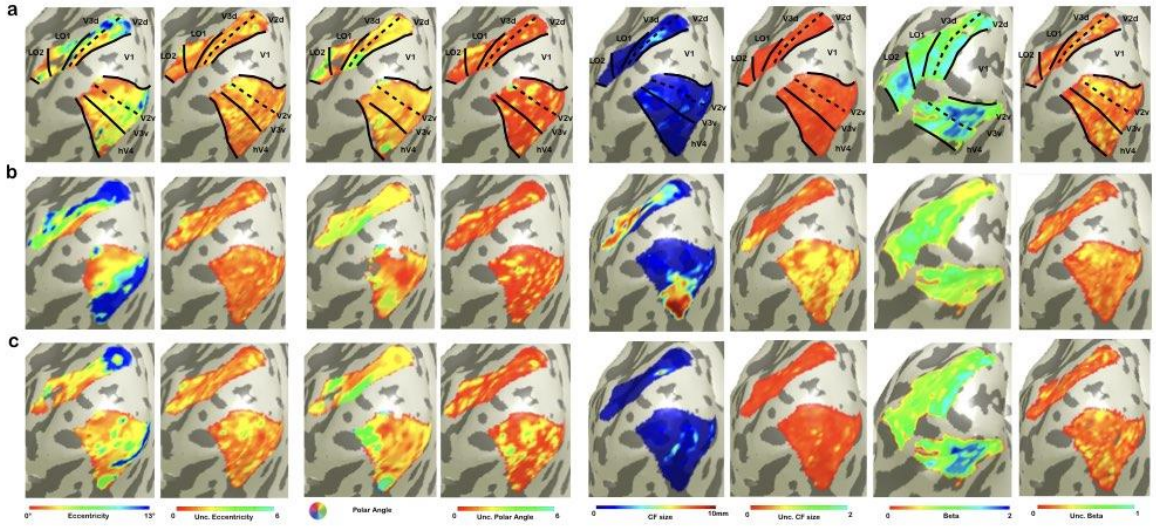


Figure 1 - Visualisation of uncertainty for CF parameters at single subject level. Panel A corresponds to SD derived estimates. Bottom panels B and C show uncertainty estimates for each RS run.

Disclosures: A. Invernizzi: None. **K.V. Haak:** None. **J. Carvalho:** None. **R.J. Renken:** None. **F.W. Cornelissen:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.06

Topic: D.07. Vision

Support: ERC-2017-PoC grant (779860)

Title: Real-time pRF mapping using gradient descent on hashed-gaussian tiles

Authors: S. BHAT[1], M. LÜHRS[1], R. GOEBEL[2], *M. SENDEN[1];
[1]Maastricht Univ., Maastricht, Netherlands; [2]Fac. of Psychology and Neurosci., Maastricht, Netherlands

Abstract: Population receptive *elds (Dumoulin & Wandell, 2008, pRFs) can be used for reconstructing perceived an imagined visual stimuli such as letter shapes (Senden, Emmerling, Van Hoof, Frost, & Goebel, 2019). This may be utilized for content-based BCI letter-speller systems. To make pRFs available in a real-time unctional magnetic resonance imaging (fMRI) setting, we propose a procedure for their online estimation.
The procedure is inspired by tile coding with hashing (Sutton, Barto, et al., 1998). Tiling involves an exhaustive partitioning of input space into overlapping regions. Hashing involves a pseudo-random collapsing of a tiling into a smaller set of tiles such that individual tiles consist of non-contiguous regions. We use 2D Gaussians as tiles as they tend to produce smooth receptive *elds.
We model stimulus response as a linear combination of the overlap of tiles with that stimulus and perform gradient descent on the weights of the tiles.
We tested this procedure on previously acquired data stemming both from 3 T and 7 T MR systems each including 304 functional volumes of 755 244 and 1 463 484 voxels, respectively. We simulated the online procedure using TurboBrainVoyager^{TM}interfaced with Matlab^{TM}. Our procedure proved computationally feasible with computation time never exceeding 1 s and 1:5 s while memory consumption never exceeded 4 GB for 3 T and 10 GB for 7 T data, respectively. Raw receptive *elds can be obtained by computing the dot product between tiles and their corresponding weights and immediately used for real-time applications. It is also possible to obtain pRF parameters. The pRF location is the argmax of the raw receptive *eld while its size can be estimated from its mean intensity. Parameters in this way and o*ine mapping show good correspondence in terms of Pearson correlation (r * 0:9 for both x- and y-coordinates and r * 0:7 for *).1
References
Dumoulin, S. O., & Wandell, B. A. (2008). Population receptive *eld estimates in human visual cortex. *NeuroImage, 39* (2), 647{60. Senden, M., Emmerling, T. C., Van Hoof, R., Frost, M. A., & Goebel, R. (2019).
Reconstructing imagined letters from early visual cortex reveals tight topographic correspondence between visual mental imagery and perception.
Brain Structure and Function, 1{17. Sutton, R. S., Barto, A. G., et al. (1998). *Introduction to reinforcement learning* (Vol. 135). MIT press Cambridge.2

Disclosures: S. Bhat: None. **M. Lührs:** None. **R. Goebel:** None. **M. Senden:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.07

Topic: D.07. Vision

Support: NIH Grant R01MH111417

Title: Population receptive fields expose different somatosensory areas in humans during vibrotactile fingertip stimulation

Authors: *W. SCHELLEKENS[1], J. WINAWER[2], N. F. RAMSEY[3], N. PETRIDOU[1];
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Abstract: A goal in sensory neuroscience is to predict neuronal responses to sensory input. Population Receptive Field (pRF) modeling has been an important step forwards, describing the relation of various sensory inputs with respect to neuronal responses using simple (Gaussian) functions. In the current study, we investigate whether the pRF modeling approach can also be applied to neuronal responses caused by vibrotactile stimulation of the fingertips in humans as measured with functional MRI at 7 Tesla.
Five healthy volunteers received vibrotactile stimulation on the fingertips (frequencies: 30-190Hz). Fingertips were intermittently stimulated (i.e. 200ms on, 100ms off) for a period of 4 seconds. The order of fingertip stimulation was randomized and each digit was stimulated 24 times. We modeled the BOLD responses according to a Gaussian receptive field (RF) model, resulting in a preferred fingertip (i.e. Gaussian center) and RF size (i.e. Gaussian standard deviation) per voxel. We checked for the presence of an ordered somatotopy (i.e. spatial alignment of preferred fingertips) and RF properties within 3 pre-selected ROIs: Brodmann area BA3b/BA1, BA2, and parietal rostroventral cortex (PR), which are known to process somatosensory input.
We found a neatly ordered somatotopy in areas BA3b/BA1 and BA2 ($t_{(4)}$=5.45; p=0.006 & $t_{(4)}$=10.08; p=0.001, respectively), which was not observed in area PR ($t_{(4)}$=-0.05; p=0.520). Smallest RF sizes were measured at representations for the tip of the thumb (σ=1.53), and gradually increased towards little finger representations (σ=2.51). The RF size increase across fingertip representations was observed across all subjects ($t_{(4)}$=7.95; p=0.002), as was an RF size increase across the 3 cortical ROIs ($t_{(4)}$=6.95; p=0.003): voxels within BA1/BA3b displayed smallest RF sizes (σ=1.03), gradually increasing for BA2 (σ=2.15) and PR (σ=3.07).
In the current study, we show that pRF modeling can be applied to somatosensory cortex following vibrotactile stimulation in humans measured at 7 Tesla fMRI. We found ordered somatotopic organizations in primary somatosensory cortex, but not in higher-order somatosensory area PR. Furthermore, fingertip representations of the thumb and index finger showed smallest RF sizes, indicating high-precision processing of somatosensory input coming from these digits. RF differences between cortical areas expose different processing stages. These results show that pRF models can be used to reveal somatosensory processing stages and properties.

Disclosures: W. Schellekens: None. **J. Winawer:** None. **N.F. Ramsey:** None. **N. Petridou:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

Location: Room N427

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.08

Topic: D.07. Vision

Support: European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreements No. 641805 (NextGenVis) and No. 661883 (EGRET)

Title: Micro-probing the brain: High-resolution functional mapping of neuronal subpopulations

Authors: *J. CARVALHO[1], A. INVERNIZZI[1], K. AHMADI[2], M. B. HOFFMANN[2], R. J. RENKEN[1], F. W. CORNELISSEN[1];
[1]Univ. Med. Ctr. Groningen, Groningen, Netherlands; [2]Otto-von-Guericke Univ., Magdeburg, Germany

Abstract: Estimation of population RFs at the voxel level has tremendously contributed to progress in our understanding of the structure and function of the visual cortex in health and disease. However, due to the need to make numerous a priori assumptions about a voxel's RFs properties, the conventional approach is unable to uncover unpredicted RF shapes, a critical limitation in studies on e.g. adaptation, pathology or reorganisation. Here, we present, test and validate a novel framework, micro-probing (MP), that overcomes many of these limitations of current modeling approaches by enhancing the spatial resolution and simultaneously adding the ability to uncover unexpected RF shapes, and subpopulations. MP efficiently samples the entire visual space with micro-probes - tiny, fixed-size, gaussian models that make minimal prior assumptions - thereby creating "probe-maps": high-resolution voxel-based visual field coverage maps (figure 1B and E). These can be used to directly derive neural properties, or to extract multi-unit receptive fields (muRFs, figure 1F). We validated the method using simulations and used it to map the visual fields of both healthy participants and of a patient-group with highly abnormal RFs due to albinism. In the latter group, MP uncovered and mapped - without any specific prior assumptions - bilateral receptive fields symmetrical to the vertical meridian, characteric of these patients (figure 1A-C). Next, from these symmetry values, we could quantify the level of misrouting and identify the misrouted cortical region per observer (reddish regions in left panel of figure 1A). In controls, highly symmetric probe maps delineate only the borders of the visual areas (1A, right panel). In addition, in controls, we demonstrate how MP may reveal and map previously unknown population RFs shapes, and show these can be quite heterogeneous (figure 1D-G). We conclude that micro-probing provides a versatile and powerful high-resolution approach to uncover the functional properties of the brain, essential for linking its function to behavior and understanding its plasticity.

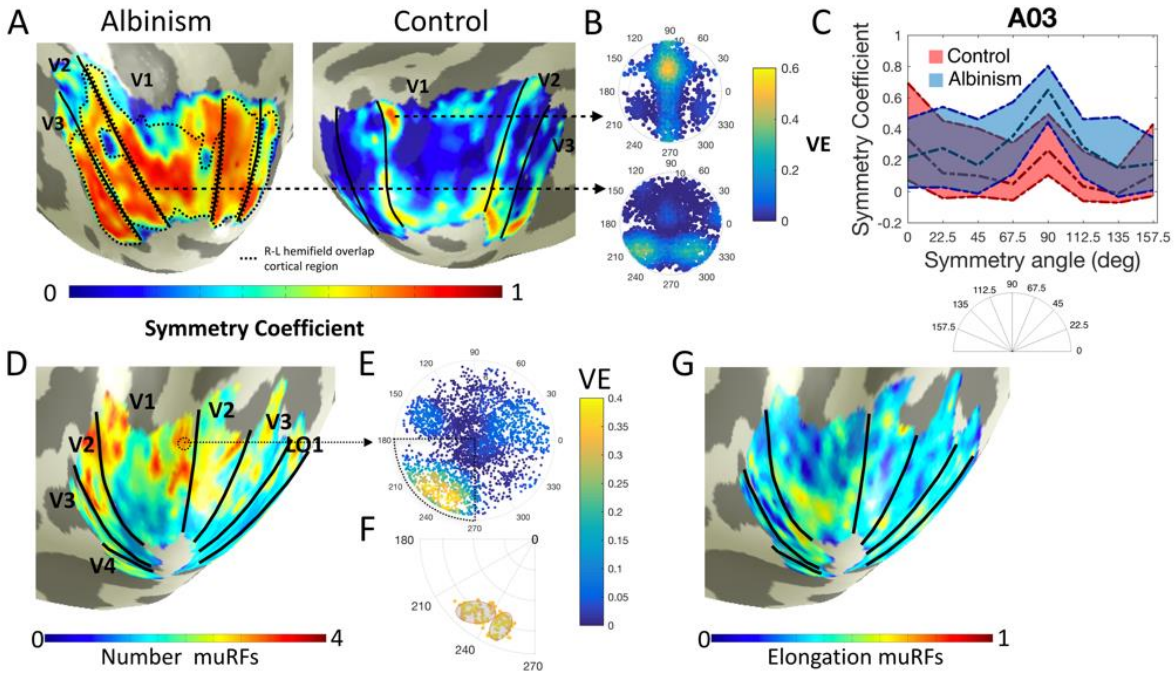

Figure 1. A: Symmetry map for the right hemisphere of the albinotic subject A03 and of the aged match control C03. The black continuous lines outline the visual areas and the black dashed line outlines the misrouted cortical region calculated based on the overlap of right and left hemifields (Hoffman et al, 2003; 2012). B: Two example probe maps for voxels of the control (top) and an observer with albinism (bottom). C: Symmetry coefficients for the V1 of the right hemisphere calculated across 8 symmetry axes (see inset). The dashed lines represent the the 5%, 50% and 95% confidence intervals. Albinotic (A03) and controls (average over 5 participants) distributions are colored in blue and red, respectively. D: Projection on an inflated brain mesh of the number of muRFs estimated per voxel (right hemisphere of observer C07). E: Example of a probe map of a V1 voxel (location indicated by the dashed circle in panel D). F: Zoomed-in view of one quarter field of the probe map indicating the estimated muRFs (outlined by a red dashed line). G: Projection on an inflated brain mesh of the elongation of one selected muRF.

Disclosures: J. Carvalho: None. **A. Invernizzi:** None. **K. Ahmadi:** None. **M.B. Hoffmann:** None. **R.J. Renken:** None. **F.W. Cornelissen:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

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Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.09

Topic: D.07. Vision

Support: HBP grant No. 720270
HBP grant No. 785907

Title: Superficial V1 layers contain information on visual illusions, whereas mental imagery is decodable in deep V1 layers

Authors: *J. BERGMANN, A. T. MORGAN, L. MUCKLI;
Inst. of Neurosci. & Psychology, Univ. of Glasgow, Glasgow, United Kingdom

Abstract: Visual illusions and imagery are sensory experiences without corresponding physical input to the retina. Although both are internally generated, their subjective experience differs strongly. Visual illusions are under very limited volitional control; they appear embedded in our sensory environment, indistinguishable from physical reality. These characteristics stand in stark contrast to everyday mental imagery, which feels distinct and separable from incoming stimulus input. Here, we use laminar fMRI brain imaging in combination with multivariate pattern analysis to investigate for the first time how 'real' and 'imaginary' non-physical experiences are processed in the layers of primary visual cortex (V1). Connectivity to V1 follows characteristic patterns: feedforward input from the eyes arrives in mid-layers, whereas feedback from other brain areas is projected to superficial and deep layers. As a consequence, information on non-physical visual experiences should be stronger in feedback layers. Further, we want to examine whether low-level visual illusions, which result from feedback within visual cortex, display a different layer-wise information profile to mental imagery, which involves high-level feedback. We find that mental imagery is only decodable in deep V1 layers. In contrast, visual illusions are only decodable in superficial V1 layers. This pattern of results is spatially specific: using an approach informed by population-receptive field mapping, which identifies which V1 voxels represent which portion of the visual field, we show that illusory content is only decodable in the visual portions that contain the illusory contours. Likewise, mental imagery content is only decodable in the V1 region that represents the visual field portion where the participants imagine the stimulus. Our findings suggest that we can separate representations of illusory perception and mental imagery in different cortical layers of V1. This highlights the need to dissociate between lower and higher-level influences on V1 processing. The differences in layer-wise processing may also offer a new perspective on what factors may contribute to the degree with which we can exert volitional control over our experiences, and whether we perceive an experience as 'real' or not.

Disclosures: J. Bergmann: None. **A.T. Morgan:** None. **L. Muckli:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

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Presentation Number: 268.10

Topic: D.07. Vision

Support: 785907 HBP
MVLS DTP

Title: Predictive processing helps categorisation by amplifying responses to low contrast stimuli (fMRI of V1)

Authors: *G. DONNELLY[1], J. BERGMANN[1], T. LUX[1], M. BENNETT[1], L. S. PETRO[1], W. A. PHILLIPS[2], L. MUCKLI[1];
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Abstract: Context-sensitive selective amplification may help higher brain areas form predictions about the visual environment and objects within it by facilitating the processing of ambiguous or degraded visual information. Using an adapted occlusion paradigm (Smith & Muckli 2010, Muckli et al., 2015) instead of a plain occluder, we investigated how context influences behavioural and cortical responses to low contrast natural scene images, (such as a frosted screen occluding part of an image). Predictive Coding theory (Rao & Ballard, 1999) suggests predicted information is explained away and does not ascend the hierarchy (except to stabilise the internal model) whereas adaptive resonance theory (Grossberg, 2013), and coherent infomax (Kay & Phillips, 1997) imply that predicted information is enhanced. We presented subjects with natural images with the bottom right corner (the 'target' region) shown at low contrast. The image shown in the target region was either from the same scene as the surrounding full contrast image (consistent condition) or from a different image (inconsistent condition). In a psychophysical experiment, we found that the consistency between the surround and target regions affected identification, but not detection of a low contrast target image. Consistency between surround and target regions enhanced identification accuracy. In contrast, inconsistency between the regions hindered performance. This consistency effect was not only due to basic visual features, e.g. lines that continued from the surround into the target image: it was maintained even when the target and surround only belonged to the same category, but were not parts of the same image. Previous experiments show that fMRI activity patterns in parts of primary visual cortex (V1) that respond to the occluded region contain image specific feedback information. To test whether consistent information is enhanced or reduced we ran an fMRI experiment. Subjects fixated in the centre and saw 'frosted' target images in the lower right quadrant which were either identical or different to the surrounding image. Using a target image contrast at detection threshold, we found the BOLD response to the low contrast target was amplified when the full contrast surround was consistent and was reduced when it was inconsistent. BOLD imaging captures the summed energy consumption and does not separate between excitation and inhibition, nor between dendritic currents and axonal action potentials. With this caveat in mind, our findings support theories such as apical amplification and coherent infomax whereby the processing of predictable information is enhanced relative to unpredictable information.

Disclosures: G. Donnelly: None. **J. Bergmann:** None. **T. Lux:** None. **M. Bennett:** None. **L.S. Petro:** None. **W.A. Phillips:** None. **L. Muckli:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

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Presentation Number: 268.11

Topic: D.07. Vision

Support: NSF Graduate Research Development Program Grant DGE-114747
NRSA Grant F31EY027201
NIH Grant 1ROI1EY02231801A1,
NIH Grant 1RO1EY02391501A1
NIH Training Grant 5T32EY020485

Title: Differential white matter connections to ventral and lateral occipito-temporal face-selective regions underlie differences in visual field coverage

Authors: *D. FINZI[1], J. GOMEZ[2], A. A. REZAI[1], M. NORDT[1], V. S. NATU[3], B. L. JESKA[1], M. BARNETT[4], K. GRILL-SPECTOR[1];
[1]Psychology, Stanford Univ., Stanford, CA; [2]Psychology, Univ. of California Berkeley, Berkeley, CA; [3]Dept. of Neurolog. Surgery, Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Psychology, Univ. of Pennsylvania, Philadephia, PA

Abstract: The human face-processing network is organized along two distinct streams: ventral occipito-temporal cortex (VOTC) containing IOG-faces, pFus-faces, and mFus-faces, and lateral occipito-temporal cortex (LOTC) containing pSTS-faces and mSTS-faces. VOTC regions are thought to be involved in processing face identity, while LOTC regions are involved in processing dynamic aspects of faces. However, the white matter connections and computational origins constraining the organization of the face network across streams remain unknown. As face identification and dynamic perception rely primarily on foveal and peripheral vision, respectively, we hypothesized that white matter connections from early visual cortex (EVC) to ventral face-selective regions would originate more foveally than connections to lateral regions. To test this, we scanned 22 participants using 3T functional MRI and diffusion MRI. We used a functional localizer to identify face-selective regions in each participant, which were used as seed regions to functionally-define white matter tracts. Then we tested to which eccentricities in EVC these tracts connect. We found that VOTC face regions showed a higher proportion of tracts originating from the central 5° compared to LOTC regions (mean±SE: IOG-faces = .49± .01, pFus-faces = .46±.02, mFus-faces = .50±.02, pSTS-faces = .41±.03, mSTS-faces = .39±.04) whereas LOTC regions showed a higher proportion of tracts originating from eccentricities >5° than VOTC (mean±SE: IOG-faces = .51± .01, pFus-faces = .54±.02, mFus-faces = .50±.02, pSTS-faces = .59±.03, mSTS-faces = .61±.04, significant ROI x eccentricity band interaction $F(4,164) = 6.8$; $p<.001$). We next tested if these differential white matter connections across eccentricity bands contribute to visual field coverage across VOTC and LOTC face-selective regions by conducting a second population receptive field (pRF) mapping experiment (N=21). Consistent with connectivity patterns, visual field coverage in VOTC regions was foveally-biased, with the majority of pRF centers in the central 5° (proportion pRF centers: IOG-faces: mean±SE = .74±.06; pFus-faces: .71±.05; mFus-faces: .82±.07), while the majority of pRF centers in LOTC regions were located in eccentricities > 5° (pSTS-faces: .86±.05; mSTS-faces: .68±0.11). Together, these findings demonstrate that (i) the anatomical and functional segregation of face-selective regions into two streams has a structural foundation and (ii) that

differential patterns of white matter connections from EVC to face-selective regions contribute to the differential visual field coverage across processing streams.

Disclosures: D. Finzi: None. **J. Gomez:** None. **A.A. Rezai:** None. **M. Nordt:** None. **V.S. Natu:** None. **B.L. Jeska:** None. **M. Barnett:** None. **K. Grill-Spector:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

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Presentation Number: 268.12

Topic: D.07. Vision

Support: NIH Grant 1R01EY022355

Title: Goal-directed processing modulates the 2-pathway characterization of occipitotemporal and posterior parietal visual object representations

Authors: *Y. XU[1], M. VAZIRI-PASHKAM[2];
[1]Psychology, Yale Univ., New Haven, CT; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Recent studies have reported the existence of rich non-spatial visual object representations in both human and monkey posterior parietal cortex (PPC), similar to those found in occipito-temporal cortex (OTC). Despite this similarity, we recently showed that visual object representation still differ between OTC and PPC in two aspects. In one study, by manipulating whether object shape or color was task relevant, we showed that visual object representations were under greater top-down attention and task control in PPC than in OTC (Vaziri-Pashkam & Xu, 2017, *J Neurosci*). In another study, using a bottom-up data driven approach, we showed that there exists a large separation between PPC and OTC regions in the representational space, with OTC regions lining up hierarchically along an OTC pathway and PPC regions lining up hierarchically along an orthogonal PPC pathway (Vaziri-Pashkam & Xu, 2019, *Cereb Cortex*). To understand the interaction of goal-direct visual processing and the two-pathway structure in the representational space, here we performed a set of new analyses of existing data and directly compared the two-pathway separation of OTC and PPC regions when object shapes were attended and task relevant and when they were not. We found that in all three experiments the correlation of visual representational structure between superior IPS (a key PPC visual region) and ventral occipito-temporal (VOT) region (a representative higher OTC visual region) became greater when object shapes were attended than when they were not. This modified the two-pathway structure, with PPC regions moving closer to higher OTC regions and a compression of the PPC pathway towards the OTC pathway in the representational space when shapes were attended. Consistent with this observation, the correlation between neural and behavioral measures of visual representational structure was also higher in superior IPS when shapes were

attended than when they were not. By comparing representational structures across experiments and tasks, we further showed that attention to object shape resulted in the formation of more similar object representations in superior IPS across experiments than between the two tasks within the same experiment despite noise and stimulus differences across the experiments. Overall, these results demonstrated that, despite the separation of the OTC and PPC pathways in the representational space, the visual representational structure of PPC is flexible and can be modulated by the task demand. This reaffirms the adaptive nature of visual processing in PPC and further distinguishes it from the more invariant nature of visual processing in OTC

Disclosures: Y. Xu: None. **M. Vaziri-Pashkam:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

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Presentation Number: 268.13

Topic: D.07. Vision

Support: Ammodo KNAW Award (S.D.), NWO-VICI grant 016.Vici.185.050 (S.D.)

Title: Topographic maps representing haptic numerosity in the human brain

Authors: *S. HOFSTETTER[1], Y. CAI[1], B. M. HARVEY[2], S. O. DUMOULIN[1];
[1]Spinoza Ctr. for Neuroimaging, Amsterdam, Netherlands; [2]Utrecht Univ., Utrecht, Netherlands

Abstract: Numerosity, the set size of items in a group, is an innate perceptual ability with sensory attributes that guides behavior. Recently, a network of topographic maps representing visual numerosity was found in the human brain (Harvey et al.,2013, 2017). However, it is unclear whether responses in these numerosity maps are indeed dedicated abstract representations of physical quantities or reflect numerosity as a low-level visual feature. Here, we investigated this question by measuring the neural responses elicited by haptic numerosity perception, and their cortical organization. We placed varying numbers of plastic spheres (1 to 7, with a baseline of 20) in the right hands of participants while collecting ultra-high field fMRI (7T) data. The spheres were all either the same size, or the same overall volume. Participants were asked to explore the spheres, but no numerosity judgments were required. The fMRI responses were summarized using a numerosity-selective population receptive field (pRF) model, described by a logarithmic Gaussian function with two parameters: preferred numerosity and tuning width (analogous to the pRF analysis of visual field maps (Dumoulin & Wandell, 2008)). The variance explained by the model (R^2) was quantified using the residual sum of squares between the predicted and measured fMRI signals. We found neural responses that were tuned to the number of spheres placed in the hand (Fig 1A). Topographic maps of haptic numerosity responses were found in the occipital-temporal, parietal and frontal lobes, similar to

the network of the visually-driven numerosity maps (mean R^2=0.52 across 12 maps in both hemispheres, corresponding to p=0.000005, Fig 1B-C). The preferred numerosity progressed significantly with cortical distance along the maps and was well correlated between the two stimulus conditions (mean r=0.68 across 12 maps; Fig 1D). Our results show a network of haptic numerosity maps, similar to those found using visual input. These topographic numerosity maps of haptic touch hint of a network of quantity maps that is not confined to a specific sensory modality.

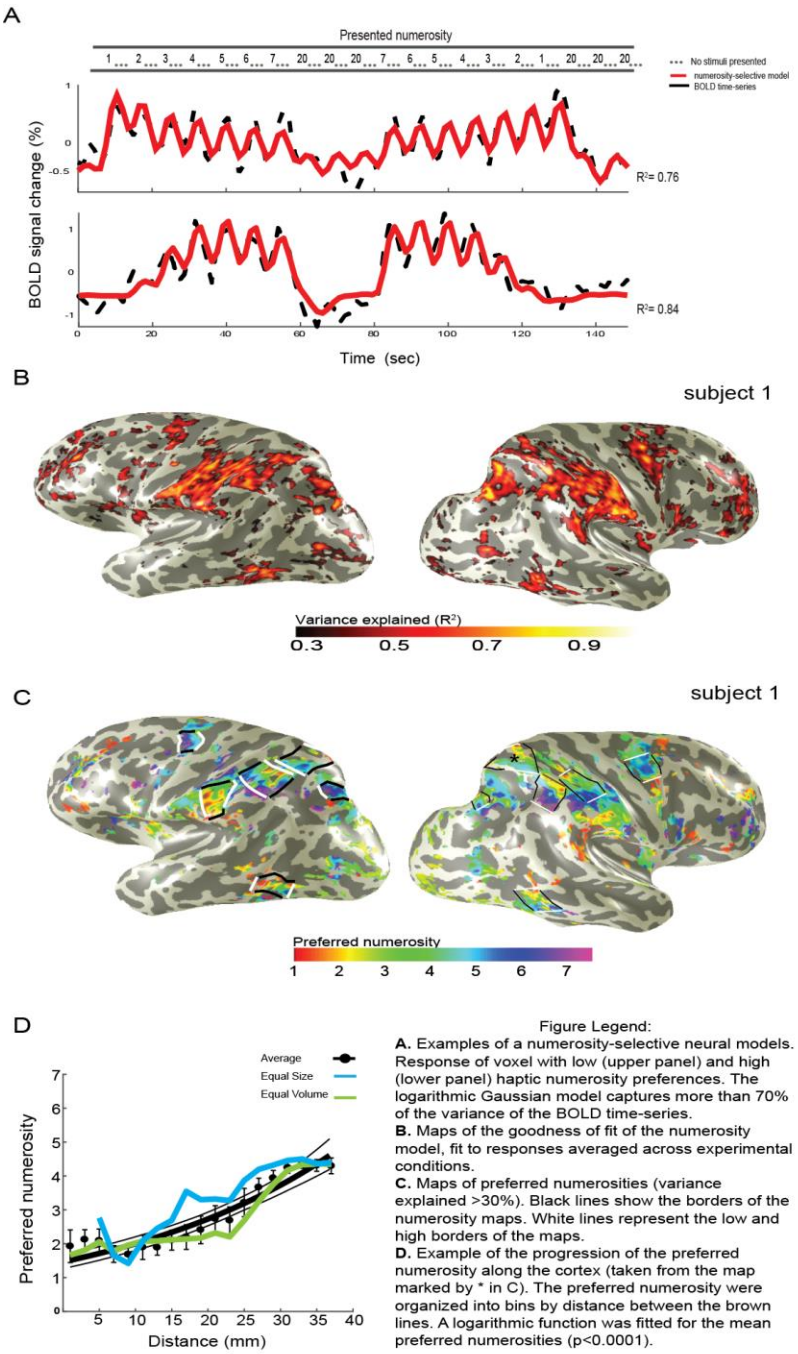

Figure Legend:
A. Examples of a numerosity-selective neural models. Response of voxel with low (upper panel) and high (lower panel) haptic numerosity preferences. The logarithmic Gaussian model captures more than 70% of the variance of the BOLD time-series.
B. Maps of the goodness of fit of the numerosity model, fit to responses averaged across experimental conditions.
C. Maps of preferred numerosities (variance explained >30%). Black lines show the borders of the numerosity maps. White lines represent the low and high borders of the maps.
D. Example of the progression of the preferred numerosity along the cortex (taken from the map marked by * in C). The preferred numerosity were organized into bins by distance between the brown lines. A logarithmic function was fitted for the mean preferred numerosities (p<0.0001).

Disclosures: **S. Hofstetter:** None. **Y. Cai:** None. **B.M. Harvey:** None. **S.O. Dumoulin:** None.

Nanosymposium

268. Organization and Function of Human Visual Cortex

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Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 268.14

Topic: D.07. Vision

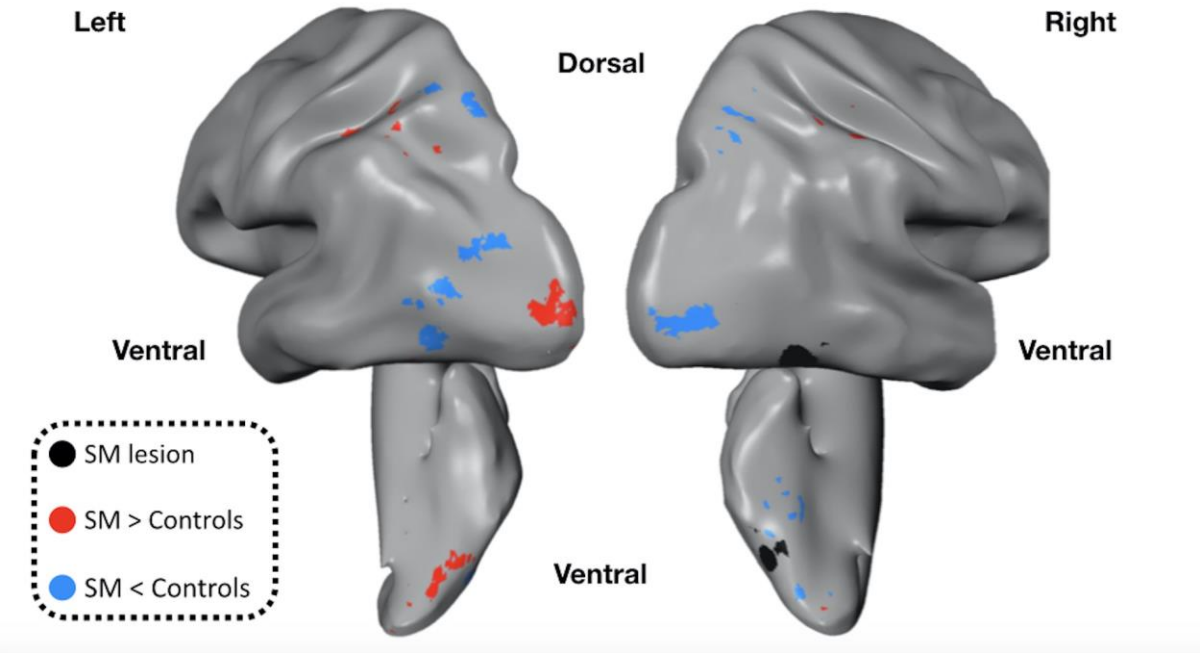
Support: Discovery Grant from the Natural Sciences and Engineering Research Council of Canada (EF)
Canada First Research Excellence Fund (VISTA)
R01EY026701 NIH (MB)

Title: Altered large-scale cortical organization of shape processing in visual agnosia

Authors: *E. FREUD[1], M. BEHRMANN[2];
[1]Psychology and the Ctr. for Vision Res., York Univ., Toronto, ON, Canada; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Shape processing is a cornerstone for various perceptual behaviors such as object recognition and face perception. Even though both dorsal and ventral pathways process shape information, a lesion to the ventral pathway alone often results in an impairment in shape perception, known as visual agnosia. This might imply that the dorsal pathway does not functionally contribute to object perception. Alternatively, it is plausible that a lesion to the ventral pathway also alters shape processing in distal regions of the dorsal pathway. To disentangle between these alternatives, in a study of a patient with object agnosia following a lesion to the right ventral pathway, we utilized a recent manipulation that has been used successfully in healthy individuals to map shape processing mechanisms (Freud, Culham, Plaut & Behrmann, 2017). As expected, shape sensitivity along the patient's right ventral pathway was markedly reduced and, as reported previously (Konen et al., 2011), a similar reduction was detected in the contralesional left ventral pathway. Of most interest, posterior parts of the dorsal pathway in both hemispheres also evinced a reduction in shape sensitivity. Finally, we identified regions in the posterior ventral pathway and anterior dorsal pathway that exhibited greater shape sensitivity in the patient compared with the controls, possibly reflecting compensatory mechanisms (Figure 1). Together, these findings demonstrate that a focal cortical lesion can lead to a large-scale reorganization of the visual cortex. These large-scale alternations are consistent with the idea that a distributed network of regions, along the two pathways, promotes shape perception.
Figure 1: Differences between patient SM and controls in the sensitivity to shape information along the dorsal and ventral pathways. Despite the focal lesion to the right ventral pathway

(black ROI), changes in shape processing were observed along the two hemispheres and the two pathways.



Disclosures: **E. Freud:** None. **M. Behrmann:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.01

Topic: F.01. Neuroethology

Support: Rowland Institute

Title: Dynamic control of motor sequences during foraging

Authors: ***J. M. LI**, D. N. ROBSON;
Rowland Inst., Harvard Univ., Cambridge, MA

Abstract: Dynamic control of motor sequences is central to animal behavior. Motor sequences are continuously adjusted in response to both the external world and the animal's own internal state. How the brain solves this dynamical control problem is a fundamental question in neuroscience. During foraging for live prey, larval zebrafish executes complex motor sequences, which are adjusted on two distinct timescales in response to the prey position and the animal's

motivational state. Using tracking microscopy, we simultaneously imaged behavior and whole brain neural activity at cellular resolution in freely swimming zebrafish for hours during foraging. We will present both a behavioral and neural model of prey capture in larval zebrafish as a nested control problem.

Disclosures: J.M. Li: None. **D.N. Robson:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.02

Topic: F.01. Neuroethology

Support: NSF Grant 1557895
NSF Grant 1557858

Title: Sensorimotor activity in midbrain circuits of a freely swimming weakly electric fish during refuge tracking

Authors: *I. UYANIK[1], N. J. COWAN[2], E. S. FORTUNE[3];
[1]Lab. for Computat. Sensing and Robotics, [2]Dept. of Mechanical Engin., Johns Hopkins Univ., Baltimore, MD; [3]Federated Dept. of Biol. Sci., New Jersey Inst. of Technol., Newark, NJ

Abstract: Sensorimotor control circuits operate in a dynamic closed loop: they receive inputs from sensory receptors, and process the signals through multiple areas in the central nervous system (CNS) to generate motor outputs, and motor outputs in turn shape the feedback received from the environment. Our goal is to describe the neurophysiological interactions between sensory and motor activity in sensorimotor control circuits to gain a fundamental understanding of the role of the CNS in biological movement and control. We performed chronic tetrode recordings in the midbrain of individual freely swimming *Apteronotus leptorhynchus,* a species of weakly electric fish, to reveal neurophysiological mechanisms underlying locomotor control. In our experiments, fish tracked the position of a moving refuge by swimming forwards or backwards during neural recordings. *Apteronotus* rely on sensory feedback for the control of this behavior—the animals sense the relative movement of the refuge and their self movement, known as sensory slip. Electrodes were placed in the Torus semicircularis (Ts), a region of the midbrain that encodes the dynamics of moving electrosensory images. Each tetrode recorded from 3-5 units per animal (17 fish). We examined sensory encoding of slip as a step toward understanding how these patterns of activity might be used in motor control by downstream circuits. Interestingly, the behavioral and neurophysiological data appear to have opposing properties. Measurements of refuge tracking behavior show that fish perform best at low frequencies (below about 0.5 Hz), matching the phase and amplitude of the movement of the

refuge, with significant degradation of performance at higher frequencies, up to about 2 Hz. In contrast, midbrain electrosensory neurons responded best to high-frequency features of moving stimuli and sensory slip. Many of these neurons respond selectivity to accelerations in sensory slip, which has higher frequency content than measures of the relative velocity or position of the refuge. Specifically, we describe direction-selective neurons that are selective for specific ranges of acceleration of the sensory slip signal. These neurons responded only to a range of accelerations of relative movement that occured within a range of velocities and within the spatial receptive field. The high-pass filtering characteristics of the sensorimotor control is of particular interest since these filtering properties match a feedback control model for the locomotor control in these fish (Cowan & Fortune, J Neurosci, 2007).

Disclosures: I. Uyanik: None. **N.J. Cowan:** None. **E.S. Fortune:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.03

Topic: F.01. Neuroethology

Support: SCGB 494712
SCGB 1004351
SCGB 543027
NIH BRAIN R01
HHMI

Title: Identifying internal states that guide natural behavior

Authors: *A. J. CALHOUN[1], J. W. PILLOW[3], M. MURTHY[2];
[2]Neurosci. Inst., [1]Princeton Univ., Princeton, NJ; [3]Psychology, Princeton Neurosci. Inst., Princeton, NJ

Abstract: Internal states can shape stimulus responses and decision-making, but we lack methods to identify internal states and how they evolve over time. To address this gap, we have developed an unsupervised method to identify internal states from behavioral data, and have applied it to the study of a dynamic social interaction. During courtship, *Drosophila melanogaster* males pattern their songs using feedback cues from their partner. Our model uncovers three latent states underlying this behavior, and is able to predict most of the moment-to-moment variation in natural song patterning decisions. These distinct behavioral states correspond to different sensorimotor strategies, each of which is characterized by different relationships between feedback cues and song outputs. Using the model, we show that a pair of neurons previously thought to be command neurons for song production are sufficient to drive

switching between states. We are currently using the model to investigate how a population of visual neurons encodes the features that drive state-switching or particular song outputs. We have also expanded this approach to investigate social interactions between more than two animals. Our results reveal how animals compose behavior from previously unidentified internal states, a necessary step for quantitative descriptions of animal behavior that link environmental cues, internal needs, neuronal activity, and motor outputs.

Disclosures: **A.J. Calhoun:** None. **M. Murthy:** None. **J.W. Pillow:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.04

Topic: F.01. Neuroethology

Support: 1U19NS104655-01
Stanford University School of Medicine Dean's Fellowship

Title: Unsupervised and continuous mapping of behavioral variation

Authors: *R. YORK[1], L. BREZOVEC[2], T. CLANDININ[1];
[1]Neurobio., Stanford Univ., Stanford, CA; [2]Neurosci., Stanford, Stanford, CA

Abstract: The neural bases of behavioral variation remain obscure. This effort requires descriptions of behavior that are accurate, comparable across groups, and - in order to be linked to neural activity - able to fully describe the temporal dynamics present in this trait. Here, we present tools for real-time monitoring, manipulation, and unsupervised description of behavior via a novel virtual reality arena for tracking the idiothetic movement of fruit flies over long periods of time. Employing this arena we measured the dynamic locomotor behavior of a cohort of over 400 individuals taken from 13 *Drosophila* species and used unsupervised high-dimensional embedding to produce a shared behavioral space capturing continuous temporal variations in locomotion. Analysis of this space showed that the general components of locomotor behavior were remarkably conserved. In contrast, individual species differed strongly - and non-phylogenetically - in their occupation of the space, reflecting both differences in behavioral frequency and possible biomechanical constraints. Taking advantage of the continuous nature of this behavioral space we identified commonly used “highways” of velocity patterns, finding that species diverged in both the routes and sequencing used in locomotion. Our results suggest that locomotion is composed of features that are deeply conserved across *Drosophila*, the sequencing and organization of which demonstrate signatures of evolutionary modification. Our framework can be extended to other systems and behaviors and provides avenues for unsupervised comparative analyses of large-scale neural and behavioral data sets.

Disclosures: **R. York:** None. **L. Brezovec:** None. **T. Clandinin:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

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Presentation Number: 269.05

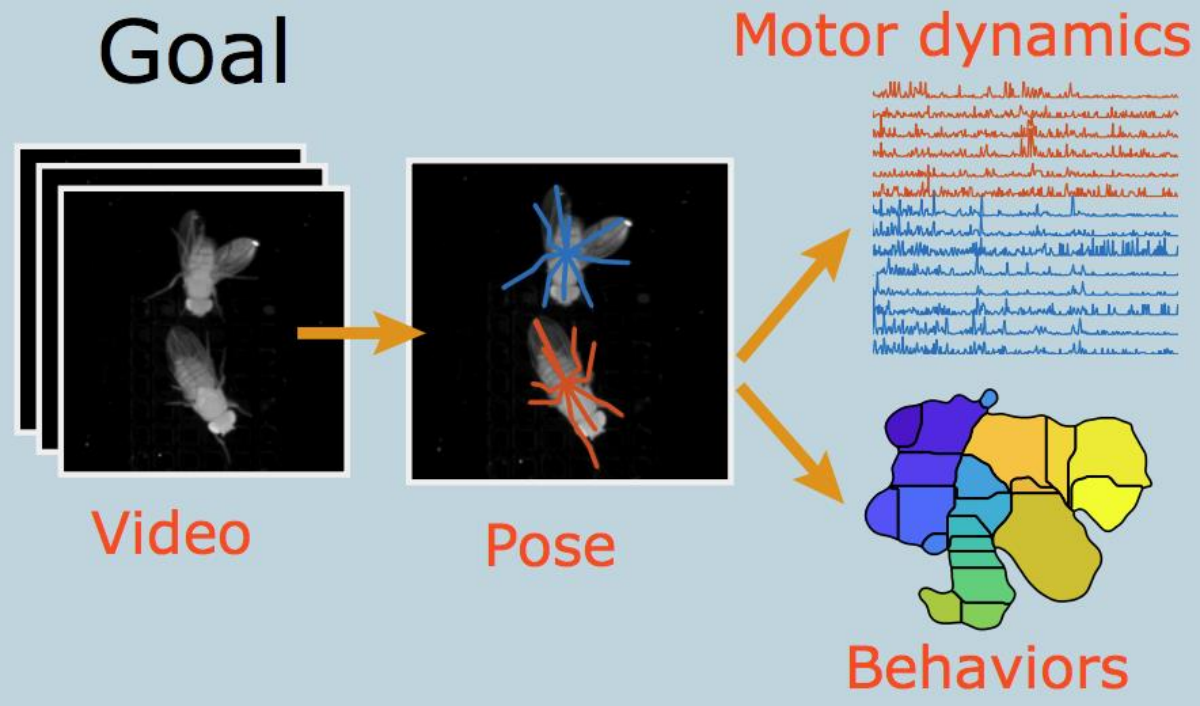
Topic: F.01. Neuroethology

Support: NSF GRFP DGE-1148900

Title: Multi-animal pose estimation using deep neural networks for social behaviors

Authors: ***T. D. PEREIRA**[1], S. RAVINDRANATH[2], J. SHAEVITZ[3], M. MURTHY[4];
[1]Princeton Neurosci. Inst., [3]Physics, [4]Neurosci. Inst., [2]Princeton Univ., Princeton, NJ

Abstract: Dissecting sensorimotor transformations in freely moving animals at the millisecond timescale requires rich representations of their motor dynamics. Recently, we developed methods to automate the estimation of animal pose from videos using deep neural networks (Pereira et al., 2019). This method, termed LEAP (LEAP Estimates Animal Pose), tracks even subtle body movements across time with high accuracy, and can be used to describe the structure of single animal behavior. Extending these techniques to a social context presents technical challenges, such as assigning body part positions to the correct animal over all time, without identity swaps. Here we present a new version of LEAP that can be trained to explicitly model the relationship between body parts, enabling accurate pose estimation in multi-individual behavioral experiments. We apply this technique to a high-resolution dataset of freely interacting male and female fruit flies to construct a map of social interactions during natural courtship. Finally, we demonstrate how patterning in these motor dynamics relate to song production and perception, providing a handle into how multimodal sensory inputs are integrated to shape complex social behaviors.



Disclosures: **T.D. Pereira:** None. **S. Ravindranath:** None. **J. Shaevitz:** None. **M. Murthy:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

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Presentation Number: 269.06

Topic: F.01. Neuroethology

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NIH Grant R01 MH118926
ARO MURI 72929-EG-MUR-01
JHU Science of Learning Institute Award
JHU Discovery Award

Title: Using augmented reality and a control theoretic approach to characterize computation of path integration in rodents

Authors: ***M. S. MADHAV**[1], R. P. JAYAKUMAR[2], S. G. LASHKARI[2], F. SAVELLI[1], J. J. KNIERIM[1,3], N. J. COWAN[2,4];

[1]Zanvyl Krieger Mind/Brain Inst., [2]Dept. of Mechanical Engin., [3]Solomon H Snyder Dept. of Neurosci., [4]Lab. for Computat. Sensing and Robotics, Johns Hopkins Univ., Baltimore, MD

Abstract: Path integration is the neural computational process that enables animals to estimate their location in an environment by integrating sensory cues that provide information about derivatives of position (velocity, acceleration etc.). This computation requires an initial estimation of position using known landmarks, measurements of self-motion, and knowledge of a path integration gain, the multiplicative factor that relates integrated self-motion cues to movement in the physical world. We built an augmented reality apparatus (the dome) to test and quantify elements of the computation of path integration in rodents. In the dome, rats run on a circular track while visual cues are projected around them. In the first set of experiments, we recorded place cells from hippocampal CA1 of individual rats while visual landmarks were moved as a function of a rat's translation velocity. When these landmarks were subsequently removed, the spatial frequency of place fields established that the path integration gain is a plastic variable that is constantly adapted using a set of reliable landmarks. (Jayakumar*, Madhav*, et al., *Nature*, 2019).
Here, we examine the role of optic flow on path integration and how it interacts with other self-motion cues. The overwhelming influence of landmarks was replaced by a set of 80 uniformly spaced vertical stripes. These stripes provided an optic flow cue but no polarizing information. In contrast to landmark manipulation, the place cell ensemble did not stay locked to the absolute position of the moving optic flow cues. In N=2 rats, the integrated position revealed by the location of place fields drifted in both the cue and laboratory frames. Nevertheless, the movement of the optic flow cues had a predictable influence on the drift of the place fields. We used system identification to fit a parsimonious, second-order model of the stochastic hippocampal dynamics (output) in response to optic flow manipulation (input). After removing the stripes, we found that optic flow had induced a recalibration of non-visual path integration gain, albeit with more variability than with landmarks.

Disclosures: M.S. Madhav: None. **R.P. Jayakumar:** None. **S.G. Lashkari:** None. **F. Savelli:** None. **J.J. Knierim:** None. **N.J. Cowan:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.07

Topic: F.01. Neuroethology

Support: NIH Grant P20 GM103650

Title: Neural and behavioral responses to naturalistic visual stimuli in the house mouse

Authors: *J. L. HOY;
Univ. of Nevada, Reno, Reno, NV

Abstract: The ability to precisely dissect neural circuits underlying behavior in the mouse has significantly enhanced our understanding of visuomotor processing in the mammalian brain. However, most studies of visual behavior and visual stimulus encoding in the mouse do not examine behavior and neural responses under closed-loop conditions where animals pursue and respond continuously to a moving target. To work towards this goal, we first quantified the behavioral responses of mice presented with small, moving stimuli within a naturalistic setting relevant to prey capture. Under freely moving conditions, mice naturally approach, freeze or avoid visual stimuli projected on a screen depending on hunger state, previous prey capture experience, or the size and speed of the visual stimulus. In alert, head-fixed mice presented with the same visual stimuli, we find that both network and single-unit activity in the superior colliculus are altered as a function of hunger state, a condition that modified behavioral responses to those stimuli under freely moving conditions. Ongoing experiments are working towards quantifying how mice respond behaviorally to moving "targets" in a closed-loop virtual reality system where the position of the stimulus is coupled to the mouse's movements. We are also quantifying how neurons in the superior colliculus and visual cortex encode motion stimuli as a function of previous prey capture experience, an additional state that significantly altered the freely moving behavior of the mouse. Thus, we are exploiting the ethological context of prey capture to monitor behavioral responses to parameterized stimulus motion in the freely moving mouse. We are working to translate these findings to a head-fixed, virtual reality preparation. In this preparation, we aim to gain additional insights into how stimulus information is encoded under conditions where the mouse is behaving continuously to pursue and respond to dynamic appetitive stimuli.

Disclosures: J.L. Hoy: None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

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Presentation Number: 269.08

Topic: F.01. Neuroethology

Support: NSF IOS-ORG 1456830
NFS EECS-1835389

Title: The shift from life in water to life on land selected for the evolution of planning circuitry

Authors: *U. MUGAN[1], M. A. MACIVER[2];
[1]Biomed. Engin., [2]Biomed. Engineering, Mechanical Engin. and Neurobio., Northwestern Univ., Evanston, IL

Abstract: Studies of animal decision making reveal two distinct, competing control paradigms: habit- and plan-based action selection. The habit system has largely been associated with the lateral striatum and its dopaminergic afferents. Conserved basal ganglia structure from lamprey to mammals suggests that habitual control evolved early and persisted through vertebrate evolution. On the other hand, the planning system requires the interaction between the hippocampus and the prefrontal cortex or its homolog in birds. While the hippocampus (and its homologs) exists in both aquatic and land vertebrates, there seems to be no known homolog of the PFC in non-mammalian aquatic vertebrates. Our prior research into the water-to-land-transition indicates large increases in both visual range and observed environmental complexity. We hypothesize that these changes advantaged neural structures promoting planning over habit. To test this hypothesis, we developed two simulations of predator-prey dynamics. First, we simulated aquatic conditions in which the prey's visual range was varied in a simple environment. Second, we simulated terrestrial conditions in which we varied environmental complexity by adding clutter and extended the prey visual range to the whole environment, except as blocked by occlusions. In both simulations, the prey was configured to have either habit-based action selection, or plan-based action selection with a preset number of states it could forward simulate. Our aquatic simulations strongly suggest that planning, while advantaged in proportion to visual range, cannot improve performance over habit in simple environments. In line with this idea, the results of our terrestrial simulations indicate that in spatially simple environments (near-open and highly cluttered) planning is not advantaged over habit. In contrast, we find that in spatially complex environments at midrange clutter level, planning produces complex predator avoidance behaviors and significantly increases performance over habit. Moreover, these results suggest that forward shifts in neural representations and the modulation of theta power in the mPFC during spatial navigation may be related to the distribution of cell connectedness. Notably, high cost choice points occur in environments that have adjacent regions of highly and poorly connected cells where planning becomes crucial. Interestingly, we find that complex environments resemble terrestrial habitats, supporting our hypothesis that a habitat shift advantaged planning over habit and is therefore likely to have been a key factor in the evolution of planning circuitry in select terrestrial vertebrates.

Disclosures: U. Mugan: None. **M.A. MacIver:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.09

Topic: F.01. Neuroethology

Support: NIH Grant K01-ES-025442

Title: Dynamic decisions and strategic repertoires in simulated multi-prey pursuit

Authors: *J. M. PEARSON[1], L. YIN[1], S. YOO[2], B. Y. HAYDEN[3];
[1]Duke Univ., Durham, NC; [2]Neurosci., Univ. of Minnesota, Minneapolis, MN; [3]Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Prey pursuit is among the most complex tasks animals perform, requiring identification and tracking of often rapidly moving prey, multi-effector motor planning, and timing and execution of capture maneuvers. Moreover, in scenarios where multiple prey are present, the choice of which individual to pursue (and when to break off pursuit) constitutes a basic ethological decision. As such prey pursuit is expected to engage multiple overlapping brain circuits in concert over multiple time scales. Here, we model multiple aspects of this pursuit behavior using a computerized pursuit task. Rhesus macaques were trained to use a joystick to move an avatar on a computer screen (circle) and were rewarded for moving this avatar to intercept one of two computer-controlled prey items (square). Prey items differed in both reward value and speed, with symbol color indicating the former. Our goal was to generate a process model: that is, we sought to predict the monkeys' movement trajectories by modeling monkeys' selection of pursuit targets and changes of mind. Using a scalable Bayesian inference approach based on variational autoencoders, we characterized monkeys' valuation and control strategies in terms of the evolution of time-varying goals—onscreen locations toward which monkeys directed their movements. Our model is capable not only of inferring these latent goals but of generating novel trajectories that capture the rich variability present in real movement. More importantly, by identifying abrupt changes in goals, our model identified apparent changes of pursuit target in a temporally precise manner, suggesting key moments about which neural dynamics are likely to realign. By aligning these inferred mental states to neuronal data collected in dorsal anterior cingulate cortex, we have begun to identify neural correlates of these mental operations. Our work thus makes analysis feasible for a new class of experimental paradigms that marry continuous movement and decision-making, opening the door to richer investigation of the neural dynamics underlying complex behavior.

Disclosures: **J.M. Pearson:** None. **L. Yin:** None. **S. Yoo:** None. **B.Y. Hayden:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.10

Topic: F.01. Neuroethology

Support: NIDA Grant DA038615

Title: Neural basis of spatiotemporally continuous action

Authors: *S. YOO, B. Y. HAYDEN;
Univ. of Minnesota, Minneapolis, MN

Abstract: To pursue a fleeing prey, a decision-maker can improve performance by computing an estimate of the predicted future position of the prey and head towards it. We studied this problem in a novel laboratory pursuit task that incentivizes prediction of future prey positions. We hypothesized that nonhuman primates will exhibit prediction for the prey position. We trained three macaques to perform a joystick-controlled pursuit task. In our task, the subjects controlled a joystick to pursue the target in open two-dimensional space on a computer screen (http://www.haydenlab.com/pursuit). The fleeing prey used an interactive escape algorithm that tracks the movement of the subject in real-time to avoid predation. We find that subjects reliably aimed towards the prey's likely future positions, indicating that they generated internal predictions and used them to guide behavior. We developed a generative model that explains real-time pursuit trajectories and show that our subjects use prey position, velocity, and acceleration to make predictions. Perhaps surprisingly, they did not take into account their own path or the walls, both of which also influenced the prey's paths. We identified a population of neurons in the dorsal anterior cingulate cortex (dACC) whose responses track the three variables that influence prediction. Moreover, neurons in dACC multiplexed these variables with a distinct and explicit representation of the prey's future position. Our results provide a clear demonstration that the brain can explicitly represent future predictions and highlight the critical role of the cingulate cortex for future-oriented cognition.

Disclosures: S. Yoo: None. **B.Y. Hayden:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.11

Topic: F.01. Neuroethology

Support: DFG RU-1847 Grant GA1475-C1
EC-H2020-FETPROACT-16 732266 WP1

Title: Neural dynamics of the fronto-parietal reach network in unrestrained rhesus macaques are not simply explained by 3D arm kinematics in a goal-directed full-body walk-and-reach task

Authors: *M. BERGER[1], N. AGHA[1], A. GAIL[1,2,3];
[1]Sensorimotor Group, German Primate Ctr., Göttingen, Germany; [2]Fac. of Biol. and Psychology,

Univ. of Goettingen, Goettingen, Germany; [3]Bernstein Ctr. for Computat. Neurosci., Goettingen, Germany

Abstract: Studies of skeletomuscular motor control often impose physical constraints in an attempt to reduce movement complexity and ease neurophysiological investigation. Yet, movements under physical constraints might be performed differently than under pure behavioral constraints, and seeming single-joint movements might not prevent muscular activities at other joints. This imposes a challenge for the analysis and interpretation of neuronal data. Leveraging markerless 3D motion capture in our recently developed Reach Cage, we test how basic neural findings from the fronto-parietal reach network in monkeys during constrained reaching behavior generalize to reaching under full-body motion.

We trained two rhesus macaques on a memory guided walk-and-reach task in the Reach Cage with precisely timed and located visual cues and movement targets in 3D space. The monkeys performed movements from the starting position to a single instructed target among two sets of four targets. One set was within immediate reach of the monkey's starting position, allowing direct reaching movements to different body-relative directions. The second set required the animal to walk towards the target before reaching. We simultaneously recorded 192 channels wirelessly at full bandwidth from six 32-channel floating microelectrode arrays implanted in parietal reach region (PRR), dorsal premotor cortex (PMd), and arm area of the primary motor cortex (M1). The animals' multi-joint movement kinematics during walking and reaching were captured using a deep neural network (DeepLabCut) and reconstructed in 3D from multiple cameras.

We could track 3D arm kinematics and self-imposed postures at the movement targets. The animals oriented their body towards the targets such that the variation of shoulder-centric arm posture at different targets was similar for reach and walk-and-reach movements. We find neural selectivity for target location during movement planning (in PMd and PRR) and execution (PMd, PRR and M1), with stronger selectivity for reach targets than for walk-and-reach targets during planning and execution. A linear decoder trained during movement planning does not generalize between reach and walk-and-reach movements, different to what would be expected for pure encoding of arm end-posture or for allocentric encoding. Additional to arm kinematics, translational head movements correlate with fronto-parietal activity. Taken together, our results argue against a strict limb-specific view of motor-goal encoding in the fronto-parietal reach network and suggest modulation of motor goal encoding by far more than just forelimb kinematics during complex movements.

Disclosures: M. Berger: None. **N. Agha:** None. **A. Gail:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.12

Topic: F.01. Neuroethology

Support: NIDA T32
NIH R01 DA037229
MN Futures Seed Grant

Title: Markerless pose estimation in freely moving rhesus macaques reveal principal components of foraging behavior

Authors: *B. R. EISENREICH[1], P. BALA[1], Y. JAFFARIAN[1], H. PARK[1], J. ZIMMERMANN[3], B. Y. HAYDEN[2];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Minnesota, Saint Paul, MN; [3]New York Univ., New York, NY

Abstract: Primates evolved to generate behavior in large three dimensional environments in which movement is unrestrained, multiple body parts move in a coordinated manner, and behavior is continuous and interactive with environmental features. The natural environment affords greater freedom of movement and demands more sophisticated multidimensional action planning. A critical barrier to understanding embodied and embedded decisions is the lack of understanding of the basic behavioral repertoire of action - something akin to a taxonomy of basic eye movement types in active vision. Identifying such a basic repertoire in turn cannot be accomplished without tools for measuring body positions that have high spatial and temporal resolution and that are practicable for use with rhesus macaques. We developed a novel computational tool that can do so, which we call Skeletor. We used this tool to measure body position (13 major joints) in individual rhesus macaque subjects placed in a large (9'x9'x8') open cage. Subjects were trained to perform a patch-leaving foraging task that incentivized movement around the entire cage. Using Skeletor we extracted the movement dynamics of subjects. We then translated the recorded joint positions into an ego centered coordinate system based on the subjects body center. This allowed us to analyze joint movements aligned to the same reference coordinate system. We performed dimensionality reduction on the sampled time series of joint positions following the approach of Stephens (2008, PlosCompBio). We find that high dimensional representations of behavior can be compressed into low dimensional states corresponding to movement and posture. These simple behavioral motifs serve to differentiate components of foraging behavior (search vs. consumption) in addition to transition dynamics.

Disclosures: B.R. Eisenreich: None. **P. Bala:** None. **Y. Jaffarian:** None. **H. Park:** None. **J. Zimmermann:** None. **B.Y. Hayden:** None.

Nanosymposium

269. Neural Mechanisms for Controlling Continuous Action

Location: Room S403

Time: Monday, October 21, 2019, 8:00 AM - 11:15 AM

Presentation Number: 269.13

Topic: F.01. Neuroethology

Title: Flexible learning of three-dimensional place contingencies in freely-moving macaques

Authors: D. C. ALLEN[1], W. ZINKE[2], S. MOTORNY[1], C. L. SUELL[1], *K. L. HOFFMAN[1]; [2]Dept. of Psychology, [1]Vanderbilt Univ., Nashville, TN

Abstract: In the field of primate neurophysiology, task stimuli and responses are typically constrained to a two dimensional plane immediately in front of a stationary individual. Under these conditions, complex cognitive tasks rules must be established and learned within this reduced environment and under heavily constrained behaviors. The primate brain, however, has evolved to support an expanded embodiment in the world that includes (i) long-range detection and foraging using high-acuity vision (ii) movement through all three dimensions in space and (iii) short-range inspection, including manual foraging and acquisition. To capitalize on these specializations in macaques, we designed a novel testing apparatus enabling flexible learning of item-in-place task contingencies that can correspond to naturalistic associations (e.g., fruit in tree, or worm in ground). The testing enclosure (5' x 5' x 7') was tiled with 16 modular wall panels, eight of which held touchscreens ('stations') that were controlled by an in-house experimental control state system. The stations were arranged in two of the four corners (NW and SE corners) in a 2-level x 2-side design. Two of 16 smaller panel openings served as reward portals, positioned opposite the active stations. Multiple camera views provided real-time monitoring and recordings for markerless position and pose tracking with DeepLabCut. Two female rhesus macaques were trained on a biconditional discrimination task in which station location (i.e., single touchscreen) indicated which of two options on the screen would be reinforced. Additionally, the corner of the enclosure (NW or SE) indicated whether reward was contingent on the location of the stimulus on the screen (location rule) or the identity/color of the stimulus (object rule). Monkeys took 7 and 11 sessions to reach criterion discrimination of each station's stimulus pairs using the object rule. The location rule was then added for stations in the opposite corner. Once both rules were learned at all stations, they were performed within the same sessions above 70% accuracy, in the one monkey tested through to criterion. From the expanded behavioral repertoire in the enclosure, we observed changes in reaching and position with learning at and across stations, and changes in when and how they collected rewards (e.g. completion of multiple trials before reward collection, and efficient trajectories to reward). The speed at which they learned the various nested task contingencies, including station- and corner-dependent rules, demonstrates the feasibility of this setup to measure complex, flexible learning -- a hallmark of primate cognition.

Disclosures: D.C. Allen: None. **W. Zinke:** None. **S. Motorny:** None. **C.L. Suell:** None. **K.L. Hoffman:** None.

Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

Location: Room S505

Time: Monday, October 21, 2019, 8:00 AM - 11:00 AM

Presentation Number: 270.01

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Discovery Fund of CAMH
CIHR

Title: Pro-cognitive and neurotrophic effects of enhancing a5-GABAA receptor functions in adult and aged mice

Authors: *T. D. PREVOT[1], G. LI[2], D. E. KNUTSON[2], J. M. COOK[2], E. SIBILLE[1];
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Abstract: Although an emotional illness, depression also involves significant changes in cognition, also frequent in aging populations. With the increasing lack of efficacy of available antidepressant treatments and the fact that none of them targets cognitive decline, the need for novel therapeutics reached a climax with the current aging population suffering from a combination of cognitive decline and depression. Altered GABA function is classically reported in psychiatric disorders and aging. More specifically, reduction of function of GABA interneurons targeting dendritic trees of excitatory cells in cortical layers contributes to cognitive and mood symptoms. α5-containing GABA-A receptors mediate the function of interneurons, hence we **hypothesize that enhancing α5-containing GABAA receptor activity will alleviate mood and cognitive symptoms in neuropsychiatric diseases and aging.** Our group developed a new positive allosteric modulator (PAM) targeting α5-containing GABA-A receptor (α5PAM), and tested its efficacy at reversing cognitive decline in mouse models of depression (n=12/group±2; 50% female) and aging (n=12/group±2). Chronic restraint stress and chronic unpredictable mild stress paradigms were used to induce depressive-like phenotypes. Multiple assays were used to attest for working memory performance (spontaneous alternation), anxiety-like phenotype (plus-maze), antidepressant-predictive activity (forced-swim test) and locomotor activity. Also, in the aging cohort, brains were harvested after chronic treatment (2months) and stained using Golgi-Cox technique. Dendritic length and spine density were quantified in the prefrontal cortex using a stereological approach (NeuroLucida). Acute and chronic administration of the novel α5PAM increased alternation rates altered in mouse models of depression ($p<0.001$ in both models) and aging ($p<0.01$), increased time spent in the open-arms of the plus-maze ($p<0.05$) and decreased the time spent immobile in the forced-swim test ($p<0.05$). Also, chronic treatment with the novel α5PAM reversed age-induced dendritic shrinkage in the Prefrontal Cortex of mice treated for 2 months. A novel α5PAM shows robust therapeutic effects (pro-cognitive efficacy, antidepressant and anxiolytic properties without sedation) in models of depression and aging, as well as disease-modifying efficacy in the aging model, making it a good candidate for drug development.

Disclosures: **T.D. Prevot:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a Patent. **G. Li:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Inventor on a Patent. **D.E. Knutson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a Patent. **J.M. Cook:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a Patent. **E. Sibille:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a Patent.

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270. Neural Mechanisms Underlying Depression and Anxiety

Location: Room S505

Time: Monday, October 21, 2019, 8:00 AM - 11:00 AM

Presentation Number: 270.02

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: IBRO
IKY-Siemens

Title: Sex differences in antidepressant response following nucleus reuniens lesion

Authors: *C. DALLA[1], **V. KAFETZOPOULOS**[1,2], H. LEITE-ALMEIDA[3], I. SOTIROPOULOS[3], N. SOUSA[3], K. ANTONIOU[4], N. KOKRAS[1];
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Abstract: Sex differences are evident in stress response, depression and antidepressant response. Forced Swim Test (FST) is widely used as a test for antidepressant potential with marked sex differences. We have shown recently in male rats that the circuit prefrontal cortex (PFC) and hippocampus, is essential for the FST behavioral response. The hippocampus projects directly to the PFC, whereas the reverse connection is relayed through *nucleus reuniens* (RE). In the present study, adult male and female Wistar rats were anesthetized and placed in a stereotaxic frame and an infusion of 0.6 μl of 100 mM NMDA or vehicle was performed directly into the RE. One week later RE-lesioned and sham-operated rats were forced to swim for 15 min during a pretest session and 24 h later were subjected again to a 5-min FST, test session. Rats were given an i.p injection of sertraline (SSRI, 10 mg/kg) or clomipramine (a tricyclic antidepressant, 10 mg/kg) or vehicle at 23, 5 and 1 h before the FST test. All females were tested and sacrificed in diestrous phase of the cycle. 90 min after FST, animals were perfused and c-FOS immunostaining was performed on their brain. Neurons that were c-FOS-immunoreactive were counted in the RE, the PFC and hippocampus using StereoInvestigator software. Regarding FST behavioral response, vehicle-treated, sham-operated females exhibited higher immobility duration than males. As expected, sertraline and clomipramine exerted an antidepressant effect by reducing immobility in

sham-operated male and female rats. Sertraline also increased the duration of swimming behavior in both sexes, whereas clomipramine enhanced climbing. Interestingly, lesion of the RE resulted in increased swimming and decreased immobility duration, in comparison to sham-operated rats, in both sexes. Sertraline also reduced immobility in RE-lesioned female rats. Moreover, in males, RE lesion enhanced head shakes compared to sham operation. Evidently, RE lesioning displayed an antidepressant-like behavioral response in the FST closer to sertraline's than clomipramine's action. Moreover, alterations in PFC activation after FST, measured by c-FOS immunoreactivity, were more pronounced in female rats. The effects of sex and antidepressant treatment was more evident in the left part of the PFC, while there was no difference between hemispheres in the hippocampus. In contrast, RE activation was lower in female than sham-operated males. These findings point to a sex-differentiated antidepressant response of the hippocampus-RE-PFC circuit, which is influenced by the mechanism of action of the antidepressant compound tested.

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270. Neural Mechanisms Underlying Depression and Anxiety

Location: Room S505

Time: Monday, October 21, 2019, 8:00 AM - 11:00 AM

Presentation Number: 270.03

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: TUBITAK BIDEB 2232

Title: Effects of subchronic oral ketamine on behavioral despair and spatial memory in rats

Authors: A. ECEVITOGLU, R. CANBEYLI, ***G. UNAL**;
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Abstract: Ketamine, a non-competitive NMDA receptor antagonist used as a major anesthetic agent, has been suggested as a promising alternative to classical pharmacological agents targeting the monoaminergic system in depression treatment. Studies in rodents and clinical populations showed that intravenous or intraperitoneal administration of ketamine leads to a rapid-onset antidepressant effect. This result was repeated in pilot clinical studies utilizing oral administration of ketamine. The key issue is to sustain the antidepressant effect of ketamine in long-term use while minimizing its cognitive side effects. We investigated the effects of subchronic (10 to 30 days) oral ketamine on behavioral despair and spatial working memory in adult male Wistar rats. Ketamine (0 mg, 0.2 mg or 0.4 mg) was mixed with apple-juice and provided *ad libitum* in animal cages. Following 10 days of ketamine administration, rats were tested for behavioral despair in the forced swim test (FST). They were then food-restricted for 12

days and tested in a 5-day long Y-maze for spatial working memory. The animals were injected with 5'-Bromo-2'-Deoxyuridine (BrdU) to assess potential differences in hippocampal neurogenesis. Water and ketamine consumption of the groups (no ketamine control, 0.2 mg ketamine, 0.4 mg ketamine) did not differ before and after behavioral testing (*p*s > .05). We observed an antidepressant effect of 10-day consumption of ketamine in the 0.4 mg ketamine group, but not the controls (no ketamine) or 0.2 mg ketamine animals, as measured by significantly less immobility on the test-day of the FST ($p < .001$). Nineteen out of twenty-four rats learned the Y-maze by the 5th test day, during which the overall time spent in the maze dropped significantly ($p < .001$). We did not find an effect of ketamine at given concentrations on spatial working memory as the performance of all three groups improved equally well (*p*s > .05). As a result, 10-day oral consumption of 0.4 mg, but not 0.2 mg, of ketamine was able to produce an antidepressant effect without altering spatial working memory performance. Immunohistochemistry for the BrdU indicate slightly more levels of hippocampal neurogenesis in the 0.4 mg ketamine group, which may partially underlie the observed therapeutic effect.

Disclosures: A. Ecevitoglu: None. **R. Canbeyli:** None. **G. Unal:** None.

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Seed Grant Program - FSU - College of Medicine
NIMH087583

Title: CX614, a positive AMPA receptor modulator, is a better antidepressant alternative to ketamine

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Abstract: Ketamine, an antagonist of NMDA-type glutamate receptors (NMDAR) and its metabolites acting on AMPA-type glutamate receptors (AMPAR) exert acute antidepressants. Ketamine, however, has multiple undesirable physical and mental side effects while the safety profiles of its metabolites have yet to be fully characterized. Here, we provide strong evidence that a single dose of CX614 (4 and 6 mg/kg b.w.), a positive allosteric AMPAR modulator (PARM) elicits fast onset antidepressant effects that are at least as potent and long-lasting as those elicited by a single ketamine dose (10 mg/kg b.w.) in the forced swim and sucrose preference tests (FST and SPT, respectively). Both CX614 doses and ketamine produced a

statistically significant reduction in immobility in the FST and counteracted the reduction in sucrose consumption in the SPT. In vivo CX614 and ketamine treatments activate/phosphorylate TrkB, mTOR, ERK and AKT/PKB with CX614's effects on the phosphorylation of these molecules being dose-dependent. In addition, hippocampal tissue collected from ketamine- and CX614-treated rats and ketamine- and CX614-treated acute hippocampal slices were used to compare signaling pathways activated by both drugs. The results indicated that both drugs increased activation/phosphorylation of protein translation regulatory molecules, such as mTOR, ERK, AKT/PKB and 4EBP1, and upregulated expression of the immediate early gene ARC. In addition, CX614 treatment of acute hippocampal slices increased the phosphorylation of SSH1, cofilin, LIMK and GluR1. Taken together, our results infer coupling between protein synthesis, actin polymerization and GluR1 trafficking following CX614 treatment. Further elucidation of the implicated signaling cascades that link protein translation with cytoskeletal actin regulation revealed a critical role for the protease calpain as regulator of both translation and actin polymerization, both of which consolidate synaptic structural and protein translation-dependent plasticity. Our results have implications for the use of CX614 as a new fast-onset antidepressant. Considering the highly significant correlation between depression and cognitive impairment, our results afford added value in the treatment of cognitively impaired and/or depressed patients.

Disclosures: H. Jourdi: None. **M. Kabbaj:** None.

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270. Neural Mechanisms Underlying Depression and Anxiety

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Presentation Number: 270.05

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NSERC DG to LK
NSERC DG to HC

Title: Impact of ketamine on fear memory extinction and hippocampal protein expression in a preclinical model of depression

Authors: J. JOHNSTON[1], B. KULYK[2], R. ROMAY-TALLON[1], H. CARUNCHO[1], *L. E. KALYNCHUK[1];
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Abstract: Chronic stress plays an important role in the pathogenesis of major depressive disorder through abnormally elevated glucocorticoid levels. Prolonged exposure to the corticosterone produces a number of depression-like behaviors in rats, including making extinguished negatively-valenced associations more prone to reinstatement in a contextual fear

conditioning and extinction paradigm. This bias is difficult to treat, with certain traditional antidepressants worsening this symptomology. In this study we investigated the effects of chronic exogenous corticosterone exposure on auditory fear conditioning and extinction, and evaluated the efficacy of the recently approved fast-acting antidepressant ketamine in modulating long-term fear and extinction recall in repeated CORT-treated rats. In addition, we determined the impact of ketamine on reelin and doublecortin expression in the subgranular zone of the hippocampus. Rats received 40 mg/kg injections of CORT for 21 consecutive days. Following repeated CORT/vehicle treatment, all animals underwent a fear conditioning paradigm. 15mg/kg of ketamine was administered 60min prior to extinction training. Reelin-ir and doublecortin-ir neurons were quantified in the subgranular zone of the hippocampus to determine specific neurobiological effects of ketamine. Regardless of prior CORT exposure, pre-extinction administration of a subanesthetic 15 mg/kg dose of ketamine induced an immediate and substantial attenuation of cue-elicited freezing during conditioned fear recall assessment. Chronic CORT administration decreased levels of reelin expression, which were rescued through an acute dose of ketamine, though levels of DCX were not rescued.The present study therefore demonstrates that chronic exposure to the glucocorticoid CORT induces a failure of long-term extinction retrieval and establishes ketamine as a powerful modulator of fear memory, emotionally-driven behavior, and hippocampal reelin expression, which brings about an interest in the study of putative common pathways of ketamine and reelin perhaps through the modulation of mTOR signaling.

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Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

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Presentation Number: 270.06

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NSERC DG to HJC
NSERC DG to LEK

Title: Cyclical corticosterone administration as an animal model of recurrent depression results in aggravation of depression-like behaviour and accompanying changes in neurobiological markers

Authors: J. ALLEN[1], K. A. LEBEDEVA[2], E. KULHAWY[3], L. KALYNCHUK[1], *H. J. CARUNCHO[1];
[1]Div. of Med. Sci., Univ. of Victoria, Victoria, BC, Canada; [2]Univ. of Saskatchewan, Saskatoon, SK, Canada; [3]Life Sci. Innovation Hub, Calgary, AB, Canada

Abstract: Depression is the most prevalent psychiatric disorder and is characterized by a cyclical disease course with repeated episode relapses. Depression can be modelled using a corticosterone (CORT)-administration paradigm; CORT-treated rats exhibit depression-like behavior that is associated with decreased hippocampal reelin and neurogenesis. Furthermore, Repressor Element Silencing Transcription factor (REST) and microglia are suspected to be involved in the pathogenesis of depression through regulating stress, neurogenesis and neuroinflammation. In this experiment, we modelled the episodic nature of depression using repeated cycles of CORT exposure, interspersed with recovery periods. We reasoned that episode relapse in depression patients may be due to the individual becoming increasingly sensitized to stress, and that exposing rats to repeated cycles of CORT exposure might be a productive way to examine this idea experimentally. Long-Evans rats received repeated and intermittent CORT administration (three cycles of 21 days of injections at 20mg/kg, each one followed by a 21-day recovery period). Naïve animals were subjected to the forced swim test (FST) at specific timepoints to examine depression-like behavior, followed by immunohistochemical analyses of hippocampal reelin, REST, neurogenesis and microglial cell morphology. Our results demonstrate that CORT produced an increase in depression-like behavior which was paralleled by a decrease in the expression of reelin. CORT-induced FST-immobility recovered to baseline levels after the first two recovery periods, but not after the third recovery period. Reelin was downregulated by CORT during the first cycle of treatment and after the 21-day recovery period, and this downregulation was more pronounced in cycle three and after the recovery period. Deficient neurogenesis was seen after the first recovery period and after 21 days of CORT in cycle 3, however, after the third recovery period the levels were recovered. CORT also decreased the number of REST+ cells and altered the morphology of microglia. Our data provide evidence that alterations in the expression of hippocampal reelin, neurogenesis, REST and microglial cell morphology are important neurochemical events underlying depression-like behavior. In addition, that repeated and intermittent CORT treatment can be used as an animal model of recurrent depression, with the animals sensitizing to stress over subsequent cycles of CORT exposure.

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Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

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Presentation Number: 270.07

Topic: G.05. Anxiety Disorders

Support: NIH Grant MH115536
NIH Grant GM080202

Title: Endocannabinoid signaling in a septohabenular circuit regulates anxiety-like behavior

Authors: *C. R. VICKSTROM, X. LIU, L.-K. YU, S. LIU, Y. HU, C. J. HILLARD, Q.-S. LIU;
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Abstract: The endocannabinoid (eCB) system can mediate anxiolysis, and exogenous cannabinoid agonists (e.g. Δ9-tetrahydrocannabinol) are frequently used for their anxiolytic effects. However, the neural circuits whereby cannabinoids exert these effects remain incompletely identified. The medial habenula (MHb) is a well-conserved epithalamic structure that is a powerful modulator of anxiety- and mood-related behavior in rodents and zebrafish and has been shown by MRI to be decreased in volume in humans with depression. We report in adult male and female mice that the eCB 2-arachidonoylglycerol (2-AG) is released from neurons of the MHb, and that this eCB release retrogradely suppresses an atypical, excitatory GABAergic synaptic input from the medial septum and nucleus of the diagonal band (MSDB). We show using viral-genetic circuit mapping, optogenetics, and slice electrophysiology that the MSDB sends a direct GABAergic projection to neurons of the ventral MHb. We observed CB1 receptor-dependent depolarization-induced suppression of excitatory GABA currents (DSE-GABA) as well as a CB1 agonist-induced suppression of GABA postsynaptic currents in MHb neurons. Using optogenetics, we show that this occurs at MSDB axon terminals in the MHb. Viral-genetic knockdown of CB1 from MSDB neurons led to anxiety-like behavior in mice and abolished DSE-GABA in the MHb, suggesting that 2-AG regulation of MSDB to MHb neurotransmission can produce anxiolytic behavioral effects. Thus, we have identified a novel circuit mechanism whereby eCBs control anxiety-like behavior.

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Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

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Presentation Number: 270.08

Topic: G.05. Anxiety Disorders

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Title: High-fat diet impact on the gut microbiota, serotonergic systems within the dorsal raphe nucleus, and anxiety-like behavior in Wistar rats

Authors: S. I. NORONHA[1,2], J. E. HASSELL, JR[2], C. STAMPER[2], M. R. ARNOLD[2], J. D. HEINZE[2], G. S. CAMPOS[1], A. R. R. ABREU[1], P. LIMA[1], M. LIEB[2], K. M. LOUPY[2], B. KARNS[2], S. JAECKEL[2], D. A. CHIANCA, Jr[1], C. A. LOWRY[2], ***R. C. DE MENEZES**[1]; [1]Federal Univ. of Ouro Preto, Ouro Preto, Brazil; [2]Dept. of Integrative Physiol. and Ctr. for Neurosci., Univ. of Colorado Boulder, Boulder, CO

Abstract: High-fat diet (HFD) consumption has been related to development of obesity, which in turn is associated with several chronic health conditions, including cardiovascular diseases, type 2 diabetes, chronic low-grade inflammation, and psychological disorders such as anxiety disorders. Further, HFD is associated with gut dysbiosis. Obesity could potentially create a vulnerable condition, resulting in gut dybiosis, altered microbiome-gut-brain axis signaling impacting brainstem serotonergic systems, and facilitating chronic anxiety-like states or exaggerated anxiety-related defensive behavioral responses; however, the relationships among HFD-induced obesity, gut microbiota dysbiosis, serotonergic systems, and anxiety-related defensive behavioral responses are not completely understood. To test the hypothesis that obesity involves changes in the gut microbiota, impacts brainstem serotonergic systems within the dorsal raphe (DR) nucleus, and induces anxiety-like defensive behavioral responses, we exposed rats to a 9-week HFD-induced obesity protocol (45% fat; kcal/g) or a control diet (CD; 11% fat; kcal/g). Gut microbiome analyses were done using 16S rRNA gene sequencing, and alpha diversity, beta diversity, and relative abundance metrics were used to describe microbial community diversity and community structure in HFD-fed and CD-fed rats. Effects of HFD on brainstem serotonergic systems were evaluated using *in situ* hybridization histochemistry for analysis of mRNA encoding the rate-limiting enzyme in the synthesis of serotonin, tryptophan hydroxylase 2 (*tph2)* and the high-affinity, low-capacity serotonin transporter (*slc6a4)*. We investigated anxiety-related defensive behavioral responses using the elevated plus-maze (EPM). We found that HFD-fed rats, relative to CD-fed rats, showed decreased overall α diversity as assessed by Observed OTUs and altered gut microbiome composition as assessed by PERMANOVA ($p <$ 0.0001).HFD-induced obesity and gut dysbiosis were associated with increased *tph2*($p <$0.0001) and *slc6a4* ($p <$0.0001)mRNA expression within the overall DR and within subregions of the DR involved in the control of anxiety-like defensive behavioral responses. Finally, HFD-fed rats had increased anxiety-related defensive behavioral responses when tested in the EPM, as measured by decreased latency to enter the open arms and relative number of entries into the open arm of the apparatus. These data are consistent with the hypothesis that HFD-induced obesity alters brain serotonergic signaling, leading to development of a chronic anxiety-like state and increased anxiety-like defensive behavioral responses.

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Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

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Topic: G.05. Anxiety Disorders

Support: NIMH R01MH103848
NINDS R01NS073899

Title: Early life stress and FKBP5 interact to enhance anxiety-like symptoms and affect AKT signaling in young adult mice

Authors: *M. CRIADO-MARRERO, N. GEBRU, L. GOULD, C. A. DICKEY, L. J. BLAIR; Dept. of Mol. Med., Univ. of South Florida, Tampa, FL

Abstract: The FK-506 binding protein 5 (FKBP5) is a key regulator of the stress response through binding and inhibition of the glucocorticoid receptor (GR). Stress-induced changes in this protein, at the gene and protein levels, can increase GR resistance and hypothalamic pituitary adrenal (HPA) axis sensitivity. These are known as physiological hallmarks for mental health disorders such as anxiety and depression. Although clinical studies have reported a significant association of FKBP5 polymorphisms and early life stressors on increasing the susceptibility to develop neuropsychiatric disorders, the mechanisms by which stressors affect FKBP5 have not been fully elucidated. We hypothesize that the interaction of early life stress and high FKBP5 levels may induce long-lasting changes in the brain directly affecting cognition and emotions. To test this hypothesis, we used an early life stress model (maternal separation 3 hrs daily for 14 days) to assess whether FKBP5 overexpression in the brain increases vulnerability to affective symptoms. We observed that early life stress increased anxiety levels in young adult transgenic mice overexpressing FKBP5 (rTgFKBP5). When compared to males, rTgFKBP5 female mice showed greater disruption on learning and memory processes. We also found a significant reduction of AKT phosphorylation at Ser473 in the dorsal hippocampus, but not in the ventral hippocampus or amygdala brain areas. These findings have a significant impact on our understanding of the biological mechanisms underlying gene*environment interactions, which may lead to improved therapies for adolescents and adults to treat anxiety and other mood-related illnesses.

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270. Neural Mechanisms Underlying Depression and Anxiety

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Topic: G.05. Anxiety Disorders

Support: NIMH Grant R01 MH096093
NIH Grant 5K12 GM088021
Harvey Family Endowment (ELB)

Title: Evolution from fear to anxiety: Live imaging of brain states and role of the serotonergic system

Authors: *D. R. BARTO[1], T. W. USELMAN[1], E. L. BEARER[1,2];
[1]Dept. of Pathology, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Life threatening fear induces anxiety states in a subset of vulnerable individuals and may persist for their lifetime. How fear impacts the brain's neural activity and how this activity resolves or progresses over time is unknown. Sustained activity in fear-associated brain nuclei may be a factor in the development of anxiety. Here we take a novel longitudinal 3D imaging approach, manganese-enhanced magnetic resonance imaging (MEMRI), to observe *in vivo* neural activity throughout the living whole brain--from resting state, to threat (predator stress (PS) provoked by 2,3,5-trimethly-3-thiazone, TMT), to progression or resolution. To identify neural correlates of fear-like and anxiety-like states, we compared brain activity of wild type (WT, C57/b6) mice (n=12) with that of serotonin transporter knockout mice (SERT-KO) (N=12). The SERT-KO mice display persistent defensive behavior in the absence of threat (Adamec et al. 2006), a form of "anxiety". Thus difference in neural activity between WT and SERT-KO at 9 days post PS may identify neural correlates of an anxiety-state. Both KO and WT mice had equivalent exploration at baseline, and both reacted to PS with statistically significant decrease compared to baseline ($p<0.001$ by Dunnett's test). While WT returns to baseline exploration subsequent to the PS, SERT-KO does not ($p<0.0001$ at 24 days post PS). To image neural activity corresponding to these behaviors, mice received intraperitoneal injections of Mn^{2+} (0.3mM/kg). Mn^{2+} enters neurons through voltage-gated Ca^{2+} channels producing a hyper-intense signal in active neurons. Statistical parametric mapping within groups detected altered activity in select regions throughout the brain, which evolved between time points: resting state, immediately after PS and 9 days later ($p<0.0001$). Patterns of activity differed between genotypes, with higher levels and more segments involved in SERT-KO than WT. Using a new MR-based segmentation atlas we identified activated subregions and quantified differences between them at each time point. Results were visualized anatomically, and with column graphs and heatmaps. The degree of intensity differences in the most significant subregions were measured and compared statistically between groups by ANOVAs. At 9 days after fear exposure the striatum in the SERT-KO, including the nucleus accumbens, substantia innominata, and fundus of striatum, had elevated Mn^{2+} compared with WT($p<0.05$, FDR corrected). These results identify brain regions involved in immediate fear response and its evolution into sub-cortical nuclei that correlated with persistent defensive behavior in the absence of threat.

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Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

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Topic: G.05. Anxiety Disorders

Support: NIMH Grant R01 MH096093
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Title: Serotonin transporter lacking mice are resilient to anxiety after early life adversity: Using MEMRI to obtain a bird's-eye view of the brain

Authors: ***T. W. USELMAN**[1], D. R. BARTO[1], R. E. JACOBS[2], E. L. BEARER[1,3]; [1]Dept. of Pathology, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Zilkha Neurogenetic Inst., USC Keck Sch. of Med., Los Angeles, CA; [3]Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Adverse early life experience can disrupt the brain's intricate circuitry important for normal function. The monoaminergic systems consist of brain-wide modulatory projections, responsible for the regulation of experience in normal brain physiology and behavior. Additionally, monoaminergic reuptake transporters have been common pharmacological targets in the treatment of affective disorders. Here, we investigate the evolution of neural-activity in wild-type (WT) and SERT knockout (SERT-KO) mice exposed to early life stress (ELS) upon a single exposure to fear (2,3,5-Trimethyl-3-thiazoine, TMT). Complementary behavior analysis, found defensive behavior of WT (n=12) animals 9 days after fear increased compared to baseline, while SERT-KO (n=13) animals returned to baseline. To examine neural-correlates of this behavior, a holistic brain imaging modality, Mn^{2+} enhanced MRI (MEMRI) was utilized. Mice were given intraperitoneal injections of Mn^{2+} (0.3mM/kg), which enters voltage-gated Ca^{2+} channels indicating neuronal activity measured via hyper-intense T_1 MR-signal. Statistical parametric mapping revealed differential activity of WT animals across time points and universally between genotypes ($p<0.0001$). Automated brain segmentation analysis developed from an MR-based atlas was used to identify differential activity within regions of interest. WT animals display increases in day 9 activity in the substantia insomniatia, medial habenula, nucleus accumbens, and the locus coeruleus. SERT-KO animals showed resiliency to this persistent activity, with no difference from resting state. Furthermore, noradrenergic and serotonergic projection histology showed decreased arborization in the medial prefrontal cortex and nucleus accumbens of mice exposed to ELS. Together, our data finds that early life adverse experience disrupts serotonergic circuitry and increases susceptibility to anxiety. Globally decreased synaptic reuptake of serotonin correlates with improved outcome. Lastly, this study

demonstrates the use of MEMRI as a powerful tool using whole brain neuronal activity to uncover brain pathophysiology.

Disclosures: T.W. Uselman: None. **D.R. Barto:** None. **R.E. Jacobs:** None. **E.L. Bearer:** None.

Nanosymposium

270. Neural Mechanisms Underlying Depression and Anxiety

Location: Room S505

Time: Monday, October 21, 2019, 8:00 AM - 11:00 AM

Presentation Number: 270.12

Topic: G.05. Anxiety Disorders

Support: NIMH Grant R01 MH096093
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Title: Evolution of brain states: Brain-wide imaging and role of neuromodulatory systems

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Abstract: Emerging technologies allow whole brain imaging and electrophysiology of the living brain. Results are changing our concepts of how various brain regions integrate for coordinated processing to produce emotional states evidenced by behavior. Manganese-enhanced magnetic resonance imaging (MEMRI) is one of these technologies. The brain is transparent to MR, hence the whole brain can be imaged live at 50-100μm^3 resolution. Mn^{2+}, a calcium mimetic, highlights active neurons by entering through voltage-gated calcium channels and is then detected by T_1-weigthted MRI. Unlike BOLD MEMRI is direct indicator of neural activity. By histopathology, electrophysiology and behavioral criteria, Mn^{2+} is non-toxic, and thus MEMRI permits repeated imaging sessions. By repeated imaging, we obtain longitudinal information of brain-state evolution and can correlate brain activity with behavioral states over time. Because Mn^{2+} uptake requires minutes to hours to be detectable, neural activity occurring in awake, behaving animals is detected after the conclusion of an experiment. We have developed computational processing to extract statistically significant information from cohorts of genetically identical mice experiencing similar experimental procedures and a new MR-based segmentation atlas of the living brain. Companion optical imaging of c-Fos staining acquires higher spatial and temporal resolution in active brain regions identified by MEMRI. We have applied these approaches to discover how monoaminergic systems affect medial prefrontal cortical (mPFC) projections and

whole brain activity. Monoamine neuromodulatory systems are the main targets for pharmacologic interventions in affective disorders. Using mice with monoamine transporters knocked out (NET, SERT, DAT), we discovered the impact of these systems on mPFC functional anatomy before and after acute fear experience. While NET-KO decreases deeper projection activity, SERT-KO has the opposite effect. New computational alignments demonstrate overlap of mPFC projections with regional activity, suggesting a causal realtionship. This presentation will focus on MEMRI for whole brain functional imaging in pre-clinical studies for mechanistic understanding of affective disorders.

Disclosures: E.L. Bearer: None. **D.R. Barto:** None. **T.W. Uselman:** None. **M.K. Hahn:** None. **R.E. Jacobs:** None.

Nanosymposium

271. Learning and Memory: Genes and Signaling

Location: Room S104

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 271.01

Topic: H.01. Animal Cognition and Behavior

Support: NIH P20GM103423
Pitt-Hopkins Research Foundation
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Sherman Fairchild Foundation
Bates College

Title: Tet2 is a negative regulator of DNA methylation and memory function

Authors: *K. E. ZENGELER, H. C. SMITH, A. J. KENNEDY;
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Abstract: Learning generates an epigenetic reorganization in the brain that facilitates long term memory. Active DNA methylation in the hippocampus is necessary for the formation and maintenance of memories. Here, we demonstrate that the lifetime of long-term spatial memories may be augmented via enhancing of the fidelity of DNA methylation in the hippocampus. The demethylation enzyme ten-eleven translocation 2 (Tet2) negatively regulates the function of long-term memory. The conditional knockout of Tet2 in memory-related neurons enhances 24 hr and 7 day object location memory, and preserves the fidelity of the memory beyond neurotypical capability. Whole genome bisulfite sequencing of Tet-deficient hippocampal tissue revealed hypermethylation of genes associated with plasticity and memory. These data suggest that Tet2 negatively regulates hippocampal-dependent long-term memory by demethylating the genome, and that it may be a promising therapeutic target to rescue memory impairments in disease states.

Disclosures: **K.E. Zengeler:** None. **H.C. Smith:** None. **A.J. Kennedy:** None.

Nanosymposium

271. Learning and Memory: Genes and Signaling

Location: Room S104

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Presentation Number: 271.02

Topic: H.01. Animal Cognition and Behavior

Support: BIAL 253/14

Title: Phospholipase D1 ablation disrupts dorsal-ventral hippocampal axis

Authors: ***T. G. OLIVEIRA**[1], L. SANTA-MARINHA[1], I. CASTANHO[1], R. R. SILVA[1], A. MIRANDA[1], F. V. BRAVO[1], R. CHAN[2], G. DI PAOLO[2], V. PINTO[1];
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Abstract: Lipids are major constituents of the brain and the modulation of its levels can potentially impact its functioning.We previously showed that the rodent hippocampus has a phosphatidic acid (PA) gradient along its longitudinal axis, from the dorsal (DH) to ventral (VH) poles. Since phospholipase D1 (PLD1) is a major source of PA, we tested the impact of PLD1 genetic ablation in various hippocampal dependent phenotypes that rely mainly on either the DH or VH.By mass spectrometry lipidomics we observed that PLD1 ablation affected preferentially the lipidome of the DH. To further explore this finding, we studied the impact of PLD1 ablation in a battery of hippocampus-associated behavior tasks and we observed specifically deficits in a novel object recognition task.Since PA is a central signaling lipid with membrane fusogenic properties, the modulation of its levels can potentially alter synaptic properties with an impact in neuronal structure and functioning. Therefore, we analyzed the dendritic arborization of CA1/CA3 pyramidal neurons and DG granule cells of both DH and VH. While control mice presented regional dendritic arborization identity DH-VH differentiation, these morphologic signatures were disrupted in PLD1 knock-out (KO) animals. Moreover, to explore the importance of PLD1 in the intra-hippocampal circuitry, we performed *ex vivo*hippocampal extracellular electrophysiological recordings andfound increased excitability upon long-term depression (LTD) induction in the DH of PLD1 KO animals. This major impairment in the DH was also reflected on synaptic proteins with a reduction in NR2A and SNAP25 protein levels.This is one of first studies that targets dorsal-ventral hippocampal lipidomic gradient signatures. Overall, we show that PLD1 ablation differentially affects hippocampal organization and functioning in a region specific manner, which has implications for disorders that affect learning and memory, such as Alzheimer's disease or mood disorders.

Disclosures: **T.G. Oliveira:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder - US

Patent 9,267,122. **L. Santa-Marinha:** None. **I. Castanho:** None. **A. Miranda:** None. **F.V. Bravo:** None. **R.R. Silva:** None. **R. Chan:** None. **G. Di Paolo:** None. **V. Pinto:** None.

Nanosymposium

271. Learning and Memory: Genes and Signaling

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Presentation Number: 271.03

Topic: H.01. Animal Cognition and Behavior

Support: SFB 936 to B4
The Federal State of Hamburg, "Molekulare Mechanismen der Netzwerkmodifizierung" to D.K. and O.O.
China Scholarship Council to Xiaoyan Gao

Title: Arg3.1 mediates a critical period for spatial learning and hippocampal networks

Authors: X. GAO[1], S. CASTRO-GOMEZ[1], J. GRENDEL[1], D. ISBRANDT[2], D. KUHL[1], ***O. OHANA**[1];
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Abstract: The hippocampus is important for learning and memory and for spatial navigation in adult mammals. These higher brain functions emerge during early postnatal development and mature until early adulthood. During this period, activity- and plasticity-dependent mechanisms shape hippocampal connectivity, but whether and how they affect learning memory and navigation remains unknown. Here, we present evidence that the activity-regulated and memory-linked gene Arc/Arg3.1 is transiently up-regulated in the hippocampus during the first postnatal month. To reveal whether Arc/Arg3.1 up-regulation in the neonatal mouse brain is important for learning, memory and navigation, we generated conditional Arc/Arg3.1 KO mice in which Arc/Arg3.1 was permanently removed early (Early-cKO) or late (Late-cKO) during postnatal development and compared these to constitutive KO mice. We used behavioral tests, biochemical methods and *in vivo* electrophysiology to assess spatial cognition, memory, and hippocampal network activity in adult mice. Our findings demonstrate that postnatal expression of Arc/Arg3.1 during a time window early in postnatal development is crucial for establishing proper network activity and spatial learning. In contrast, a post developmental deletion of Arc/Arg3.1 leaves learning and network activity intact. Long-term memory storage continues to rely on Arc/Arg3.1 expression throughout life. These results demonstrate that Arc/Arg3.1 mediates a critical period for spatial learning, during which Arc/Arg3.1 fosters maturation of hippocampal network activity necessary for future learning and memory storage.

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Nanosymposium

271. Learning and Memory: Genes and Signaling

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Topic: H.01. Animal Cognition and Behavior

Support: NHMRC Dementia Fellowship (T. Renoir)
NHMRC Principal Research Fellowship (A.J. Hannan)
NHMRC Project Grant (T. Renoir, A.J. Hannan)
ARC DECRA (T. Renoir)

Title: Paradoxical effects of exercise on hippocampal plasticity and cognition in mice with a homozygous null mutation in the serotonin transporter gene

Authors: J. ROGERS[1,2], F. CHEN[1], D. STANIC[1], F. FARZANA[1], S. LI[1], A. M. ZELEZNIKOW-JOHNSTON[1], J. NITHIANANTHARAJAH[1], L. CHURILOV[1], P. A. ADLARD[1], L. LANFUMEY[3], *A. J. HANNAN[1], T. RENOIR[1];
[1]Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia; [2]Biomed. Engin., Imperial Col. London, London, United Kingdom; [3]IPNP, Inserm 1266, Paris, France

Abstract: Background and Purpose: Clinical evidence has demonstrated that the serotonin transporter (5-HTT) is subject to gene x environment interactions modifying cognitive function. Voluntary physical activity (exercise) is known to improve cognitive function, but the exact synaptic and cellular mechanisms mediating this experience-dependent plasticity remain unclear. We investigated the potential role of 5-HTT in mediating these effects. **Experimental Approach**: Hippocampal CA1 long-term potentiation (LTP) and adult neurogenesis in the dentate gyrus were measured in standard-housed and exercising (wheel running) wild-type (WT) and 5-HTT heterozygous (HET) mice. The effects of exercise on hippocampus-dependent cognition were also assessed using the Morris water maze and a two-choice spatial pattern separation touchscreen task. **Key Results**: 5-HTT HET mice had impaired hippocampal LTP regardless of the housing conditions. Indeed, long-term exercise did not rescue the LTP deficit displayed by 5-HTT HET mice, nor did it change LTP in WT mice. As expected, voluntary exercise increased hippocampal neurogenesis in WT mice. However, this neurogenic effect was no longer observed in 5-HTT HET animals, even though both genotypes used the running wheels to a similar extent. We also found that standard-housed 5-HTT HET mice displayed better cognitive flexibility than WT littermate controls in the Morris water maze reversal learning task. However, 5-HTT HET mice no longer exhibited this phenotype when given access to voluntary exercise. Similar cognitive deficits, specific to 5-HTT HET mice in the exercise condition, were

also revealed on the touchscreen spatial pattern separation task, especially when the cognitive flexibility load was at its highest. **Conclusions and Implications**: Our study is the first evidence of reduced hippocampal LTP in the 5-HTT HET mouse model, confirming that serotonin signaling modulates hippocampal synaptic plasticity. We also show that functional 5-HTT is required for exercise-induced increases of adult neurogenesis. These data confirm that serotonin signaling is critical for activity-dependent neurogenesis increases through exercise. Surprisingly, long-term exercise had a negative impact on our tested hippocampus-dependent cognitive tasks, especially in the 5-HTT HET mice touchscreen location discrimination probe. Ultimately, altered 5-HTT function might heighten sensitivity to the stress component of daily exercise. Taken together, our results suggest unique complex interactions between exercise and altered 5-HT homeostasis.

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Nanosymposium

271. Learning and Memory: Genes and Signaling

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Presentation Number: 271.05

Topic: H.01. Animal Cognition and Behavior

Support: Australian Research Council Future Fellowship (FT140101327)
National Health and Medical Research Council Project Grant (APP1083334)

Title: Dissociating cognition in mice lacking neuroligins using rodent touchscreen assays

Authors: J. LUO, J. TAN, R. NORRIS, ***J. NITHIANANTHARAJAH**;
Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: Sensory information from the environment is processed at the level of synapses, the connection between neurons that form the most fundamental information-processing units in the nervous system. Neuroligins are a family of postsynaptic cell adhesion molecules that form trans-synaptic complexes critical for synapse specification, function and plasticity. Human mutations in neuroligin genes have been reported in neurodevelopmental disorders where cognitive dysfunction is a core symptom. While we have better understandings of the cellular and signaling properties of synapse proteins, detailed analyses on how key molecular players at synaptic signalling complexes regulate distinct cognitive processes has received less attention. Our recent work combining newly adapted rodent touchscreen tests with deep behavioural data analysis in mice lacking members of the neuroligin gene family (*Nlgn1*, *Nlgn2*, *Nlgn3*, *Nlgn4*) shows neuroligins play differential roles in regulating cognitive control and decision-making.

Our work is shaping the approaches and platforms necessary to expand our understandings of how synapse gene mutations alter connectivity in brain circuits essential for complex cognitive behaviours, and contribute to understanding neurodevelopmental disorders.

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Nanosymposium

271. Learning and Memory: Genes and Signaling

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Topic: H.01. Animal Cognition and Behavior

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MRC Award MR/R011567/1
Wellcome Trust Grant 108726/Z/15/Z

Title: Synaptic organization and behavior-dependent activity of mGluR8a-innervated GABAergic trilaminar cells projecting from the CA1 area to the subiculum

Authors: ***L. KATONA**[1], K. HARTWICH[1], R. TOMIOKA[2], J. SOMOGYI[1], D. J. B. ROBERTS[1], K. WAGNER[1], A. JOSHI[1], T. KLAUSBERGER[3], K. S. ROCKLAND[2], P. SOMOGYI[1];
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Abstract: Long-range GABAergic projections parallel glutamatergic pathways in cortico-cortical connectivity and are formed by specialized neurons with distinct firing patterns. In the hippocampus, some GABAergic neurons expressing somatostatin project long-distance to the medial septum and retrohippocampal areas and, together with local interneurons, contribute to dendritic inhibition of pyramidal cells in the CA1 area. A somatostatin-negative GABAergic projection neuron, the trilaminar cell, located in stratum oriens has a high level of somato-dendritic muscarinic M2 acetylcholine receptor expression and a uniquely enriched level of presynaptic mGluR8 in the input terminals. Trilaminar cells project to the subiculum besides innervating the strata oriens, pyramidale and radiatum locally. Here we characterize the synaptic connectivity and behavior-dependent activity of trilaminar cells and show that: 1) GABAergic neurons with the molecular features of trilaminar cells are present in hippocampal CA1 and CA3 in both the mouse and the rat. 2) Electron microscopic analysis showed that trilaminar cells in CA1 mostly innervate interneurons, including PV-positive cells and form synapses with specialized postsynaptic densities. 3) The majority of the mGluR8-enriched synaptic terminals on trilaminar cells are GABAergic, some originating from VIP-positive neurons. 4) In addition,

using anterograde tracing we established a subcortical input to trilaminar cells from medial septal GABAergic neurons, some of which were PV-positive. 5) Recording from GABAergic neurons *in vivo* in the hippocampus of freely moving rats, we demonstrate prolonged trilaminar cell burst firing of up to 310 Hz during slow wave sleep, but significant reduction in firing during movement, with spikes phase locked to the ascending slope of theta oscillations. As mGluR8 activation in terminals was reported to suppress transmitter release, we propose that the intermittently increased hippocampal network activity and consequent glutamate spillover during slow wave sleep leads to the suppression of GABAergic inputs to trilaminar cells, resulting in their high frequency burst discharge. We suggest that trilaminar cells support principal cells by disinhibition and coordinate the activity during offline processing between the hippocampus and the subiculum via transient inhibition of interneurons.

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Nanosymposium

271. Learning and Memory: Genes and Signaling

Location: Room S104

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 271.07

Topic: H.01. Animal Cognition and Behavior

Support: CNRS Grant

Title: Updates on Gadolinium based MRI contrast agents: Deposition, neurogenesis and cognitive impairment?

Authors: *S. M. ALKHUNIZI[1], W. ABOU-KHEIR[1], N. LAWAND[1,2];
[1]Dept. of Anatomy, Cell Biol. and Physiological Sci., [2]Dept. of Neurol., American Univ. of Beirut, Beirut, Lebanon

Abstract: <u>Background</u>: Gadolinium-based contrast agents (GBCAs) are used worldwide to enhance magnetic resonance imaging. Postmortem studies have shown that exposure to GBCAs result in Gadolinium (Gd) metal deposition in the brain. While the clinical significance of such metal deposition remains unsettled,it raises important questions concerning its long-term effects on learning and memory in developing brains undergoing multiple MRI scans. The purpose of this study is to investigate if repeated exposure to linear and macrocyclic GBCAs at young age have an impact on hippocampal neurogenesis or the spatial working memory function. It also aims at investigating if exposure to GBCAs leads to Gd deposits in the spinal cord and peripheral nerves. **<u>Methods</u>:** Young Sprague-Dawley rats were given serial daily injections of two types of GBCAs: Gadoterate-meglumine and Gadodiamide for a period of 20 days. A control group

received Saline. Along with GBCAs, animals received Bromodeoxyuridine to label dividing cells. In order to assess proliferating cellsin the dentate-gyrus (DG) of the hippocampus, one set of animals was sacrificed 48 hours after the last BrdU exposure. Furthermore, to assess the number of newly maturing neurons, another set was sacrificed 29 days after the last BrdU exposure. Hippocampal tissues were stained for $BrdU^+$and $NeuN^+$cells for confocal microscopy analysis. T-maze test was performed at day 10, day 20, and one month after the last GBCA exposure. ICP-MS was used to quantify Gd in the brains, spinal cords, and peripheral nerves. **Results:** Rats injected with gadodiamide and gadoterate-meglumine showed no significant changes in the spatial working memory performance as compared to control groups. Moreover, no significant alteration in the number of $BrdU^+$cells and $BrdU^+/NeuN^+$cells in the DG was observed. However, rats exposed to gadodiamide showed a noticeable decreasing trend in both, the rate of hippocampal neurogenesis and behavioral outcomes one month after the last GBCA injection. All GBCAs used resulted in significant Gd deposition in central and peripheral nervous tissues. **Conclusions:** Our findings indicate that Gd brain retention does not affect hippocampal neurogenesis or alter working memory function in young rats. Nevertheless, the effect of Gadodiamide exposure on hippocampal related functions and neurogenesis requires further investigation due to the decreasing trend observed. More importantly, this study provides the first evidence for Gd deposition in the spinal cord and peripheral nerves after exposure to linear and macrocyclic GBCAs. More research is needed to assess the impact of such deposition on sensory and motor neuronal activities.

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Nanosymposium

271. Learning and Memory: Genes and Signaling

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Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 271.08

Topic: H.01. Animal Cognition and Behavior

Support: National Science Foundation Graduate Research Fellowship

Title: Disambiguating the role of perirhinal cortex in perception: A biologically plausible computational approach

Authors: *T. BONNEN, A. WAGNER;
Stanford Univ., Stanford, CA

Abstract: Animals rapidly transform sensory experience into memory. In the mammalian brain, perirhinal cortex (PRC) plays a critical role in this transformation, as a medial temporal lobe structure that receives input from high-level sensory regions. Beyond its well-characterized mnemonic functions, there is an enduring debate over whether PRC is also involved in

perceptual processing. A rich empirical literature already exists, which aims to test competing accounts of the role of PRC in perception, but progress has been constrained by experimenter reliance on descriptive accounts of stimulus properties—e.g. visual "complexity," "feature ambiguity," and "high-level" perceptual demands. As an alternative approach, we begin with a biologically plausible computational model of object recognition: a convolutional neural network optimized to perform object classification from images. We demonstrate a correspondence between the model and population-level neural responses in primate inferior temporal cortex (IT), as have previously been shown; given a novel image, we largely recover the pattern of neural responses in primate IT. We then define a stimulus computable metric that formalizes the perceptual demands placed on PRC. If a linear readout of model “IT” responses is sufficient to perform a given task, it is considered to be "IT computable", not requiring further perceptual processing. By contrast, if an object recognition task is not IT-computable, yet controls perform this task, it suggests processing downstream of the ventral visual system-possibly implicating perirhinal cortex. The model is a tractable proxy for performance in a PRC-lesioned state--a stimulus computable null model for PRC function. With this approach, we evaluate stimulus sets from experiments on both sides of the debate. We find a striking correspondence between the model and PRC-lesioned subjects (r=.75). We also identify stimulus sets that may not be diagnostic as to the involvement of PRC in perception, as performance on these tasks is linearly separable in the model. This computational approach may provide a unifying account of previous experiments, and offers a step towards resolving longstanding debates in the memory literature. Future work will leverage this approach to better characterize the perceptual transformations that may occur within the medial temporal lobe.

Disclosures: **T. bonnen:** None. **A. Wagner:** None.

Nanosymposium

271. Learning and Memory: Genes and Signaling

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HHMI

Title: Sensorimotor experience remaps visual inputs to a heading direction network

Authors: *Y. E. FISHER, J. LU, I. D’ALESSANDRO, R. I. WILSON;
Neurobio. Dept, Harvard Med. Sch., Boston, MA

Abstract: We maintain our sense of direction in the dark because we can keep track of our own movements, but when visual landmarks are available, our sense of direction is even better. Moreover, we can learn new landmarks in new environments. What neural mechanisms reconcile self-movement information with ever-changing landmarks to generate a coherent sense of direction? In the *Drosophila* brain, heading direction neurons form an attractor network whose activity tracks the angular position of the fly using both self-movement and visual inputs. These heading direction neurons receive visual landmark information from a population of GABAergic neurons, called R neurons, whose receptive fields tile visual space. Using whole-cell recordings and calcium imaging from heading direction neurons, we show that each heading neuron is inhibited by visual cues in specific azimuthal positions, with different visual maps in different individuals. Inhibition arises from R neuron axons that form an all-to-all matrix of potential connections onto heading neurons. We show that matrix weights can reorganize over minutes when visual-movement correlations change in virtual reality. This reorganization causes persistent changes in the reference frame of the heading representation and can depress or potentiate visually-evoked inhibition in a manner that depends on visual-heading correlations. We propose that rapid associative synaptic plasticity between R neurons and heading neurons keeps the heading representation aligned with the external world. Computational models of grid cells and head direction networks have proposed that, by combining associative plasticity of sensory inputs with attractor dynamics that integrates self-motion, a network can establish a stable map of the world by iteratively incorporating information about consistent sensory cues. We propose that plastic synaptic connections between R neurons and heading neurons serve as this flexible anchor for the *Drosophila* heading direction system. Associative plasticity of sensory inputs, combined with attractor network dynamics, should make neural heading maps self-consistent and progressively more accurate during exploration.

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Nanosymposium

271. Learning and Memory: Genes and Signaling

Location: Room S104

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 271.10

Topic: H.01. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute

Title: The flexible generation of a stable heading representation in diverse visual scenes

Authors: *S. KIM[1,2], A. M. HERMUNDSTAD[2], S. ROMANI[2], L. F. ABBOTT[3], V. JAYARAMAN[2];
[1]Univ. of California, Santa Barbara, Santa Barbara, CA; [2]Janelia Res. Campus, HHMI, Ashburn, VA; [3]Neurosci., Columbia Univ., New York, NY

Abstract: Many animals rely on an internal representation of their bearings that must be stable enough to navigate in complex environments, yet flexible enough to adapt to a variety of different surroundings. In *Drosophila melanogaster*, heading is represented by the angular position of a localized bump of population activity of compass neurons, each arborizing in a single sector of a torus-shaped structure called the ellipsoid body. Each individual compass neuron receives inputs from a population of visual-feature-selective 'ring neurons', providing the ideal substrate for the extraction of heading information from a visual scene. Indeed, the bump position of compass neurons in the same visual environment varies across flies, and sometimes even in the same fly over time, strongly suggesting that the pinning 'offset' between landmarks in the scene and the angular position of the bump is not stereotyped, but develops over time with experience. We suggest that this variability of the pinning offset is the natural consequence of a circuit that maps arbitrary visual scenes to a stable heading representation, and hypothesize that it is realized via competitive and inhibitory Hebbian plasticity between ring neurons and compass neurons. To test our hypothesis that synaptic weights between these neurons are depressed when the neurons are co-active, we put tethered flies in a virtual reality arena and used two-photon calcium imaging and optogenetics to enforce an artificial offset between the bump position and visual landmarks. After only minutes of exposure to this artificial pairing, we found that the bump offset relative to landmark cues was shifted towards the artificially-enforced value, consistent with our hypothesis. Our results provide direct physiological evidence of population-level Hebbian plasticity in the fly compass system. This plasticity may allow animals to flexibly remap different visual environments onto stable heading representations.

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Nanosymposium

272. Basic, Theoretical, and Translational Research on Human Spatial Cognition

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Topic: H.02. Human Cognition and Behavior

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Title: Origin and distribution of grid-cell-like representations in humans

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Abstract: Grid cells in the rodent and human entorhinal cortex are a critical component of the brain's spatial navigation system. How they support spatial memory and navigation however remains unclear. In virtual-reality (VR) navigation tasks, the fMRI BOLD signal in the human entorhinal cortex is hexadirectionally modulated, which may reflect population activity of grid cells (i.e. grid-cell-like representations). Here, we first examined the neurophysiological origin of grid-cell-like representations. To this end, we tested the relationship between grid cell activity and local field potential (LFP) recordings in freely moving rats. Our results suggest that measures of population activity such as LFP can be sensitive to single-cell activity profiles, such as the orientation of the hexagonal map of grid cells. In rodents, grid cells are primarily found in superficial layers of the entorhinal cortex. In contrast, projections to the neocortex predominantly arise from deep entorhinal layers. We therefore next leveraged ultra-high field 7T fMRI to characterise the cortical depth-dependent activity profile of human grid-cell-like representations and functional connectivity to neocortical regions. These results provide novel insights into the origin and distribution of grid-cell-like representations and their relevance for navigation and spatial memory.

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Nanosymposium

272. Basic, Theoretical, and Translational Research on Human Spatial Cognition

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Presentation Number: 272.02

Topic: H.02. Human Cognition and Behavior

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Title: Mesoscopic oscillatory signals in human spatial navigation and memory - How grid like representations are modulated by perceptual input

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Abstract: Spatial navigation and memory are core activities for humans. The human brain represents spatial features of the surrounding environment (e.g. place, head direction, goal location) and of spatial activity within it (e.g. movement, speed, distance, grid) as part of performing these processes. These signals were previously observed mainly at the micro- and macroscopic level of brain organization. Recently, a series of studies used intracranial electroencephalography in humans, as they performed virtual spatial memory tasks, to also identify mesoscale representations of spatial information. Here I will further explore these representations in humans (n=77), focusing on a recent signal we found for grid-like representations, hexadirecitonal modulation of oscillatory power in the theta band (5-8Hz), which is linked to spatial memory. I will present these signals' anatomical prevalence, theories for their underlying basis and their relation to other levels of neural representation, and the way these signals are modulated by external perceptual input (e.g. navigating virtually with different levels of fog) and by internal idiothetic input (e.g. navigating in the real world with Augmented Reality). I will conclude with discussing how these mesoscale signals bridge the gap between single neuron studies and macroscopic brain signals of spatial navigation and their potential as a mechanistic basis for novel biomarkers and therapeutic targets for diseases causing spatial disorientation or memory impairments.

Disclosures: S. Maidenbaum: None. **J. Jacobs:** None.

Nanosymposium

272. Basic, Theoretical, and Translational Research on Human Spatial Cognition

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Title: Low-frequency neural oscillations code distance and temporal duration as measured with scalp EEG and hippocampal intracranial recordings

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Abstract: Past studies have demonstrated a robust relationship between hippocampal theta oscillations and spatial navigation. Such theta oscillations persist during the absence of sensory cues, and code spatial distance travelled inside teleporters (Vass et al., 2016). However, recent findings also show that time-related signals can be derived from spiking patterns of hippocampal medial entorhinal cortex neurons, suggesting the possibility of a time representation stored in the medial temporal lobe system (MacDonald et al., 2011; Heys & Dombeck, 2018). Considering these findings, it remains unclear whether theta oscillations also support perceiving and integrating time duration during active spatial navigation. To address this issue, we conducted two parallel studies, one using scalp EEG and the other hippocampal depth electrode recordings. In the scalp EEG study, we asked healthy humans to navigate through a virtual plus maze, with four target stores on an omnidirectional treadmill to better mimic real-world navigation. Participants entered teleporters that either transposed them different distances ahead for a constant amount time, or identical distances for different durations, thus allowing us to disentangle temporal and spatial information provided inside teleporters. In the iEEG study, we applied a similar design, but with the distance traveled/time spent inside teleporters jittered, thus providing a continuous assessment of distance and time representation by theta oscillations. Analyses will test whether movement-related theta oscillations (and frontal-midline low-frequency oscillations, Liang, Starrett & Ekstrom, 2018) persist during absence of sensory input, and whether oscillatory profiles can code the continuum of spatial distance traveled and/or time perceived and experienced. Our preliminary findings with scalp EEG suggest that frontal-midline low-frequency oscillations code temporal duration robustly, with weaker coding for distance. Together, these findings help to shed light on the roles of low-frequency oscillations during navigation beyond coding for movement, suggesting specific roles in coding cognitive elements of navigation.

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Nanosymposium

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Topic: H.02. Human Cognition and Behavior

Support: NARSAD

Title: Decoding spatial information from the phase of neuronal activity in the human entorhinal cortex

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Abstract: The entorhinal cortex (EC) in the human brain plays an indispensable role in allocentric spatial navigation. When monitoring the activity of EC neurons while the subject is performing spatial navigation tasks in virtual environments, about half of the neurons display spatially periodic firing patterns reminiscent of grid cell firing in the rodent medial EC. At the same time these neurons display prominent theta-nested gamma local field oscillations at 25 to 40 Hz with remarkably coherent phase relationships to their spiking activity. We have previously demonstrated that the spike-to-gamma phase relationship is spatially specific, and the iso-phase domains are concordant with the grid-like firing pattern of entorhinal cortical cells. Here we report that using a Bayesian decoding approach with the spike-to-gamma phase coherence, one can decode the avatar's movements in the environment, specifically the displacement and heading direction, from the gamma phase of the spike. We validated the robustness of the decoding against phase-randomized surrogate spike trains and demonstrated a surplus decoding power in real spike sphases. The spatiotemporal phase coherence of spikes with the local field potentials (LFP) suggests a threefold coherence of spikes to LFP, spikes to motion, and LFP to motion, self-organizing in a 2D topography. The spatially periodic topography of phase domains provide not only a spatial metric for navigation and identification of different environments with specific phase-patterns but may also explain the emergence of grid cell activity.

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Title: Single-neuron representations of spatial targets in the human medial temporal lobe

Authors: *M. TSITSIKLIS[1], J. MILLER[2], S. E. QASIM[3], C. S. INMAN[4], R. E. GROSS[5], J. T. WILLIE[6], E. H. SMITH[7], S. A. SHETH[8], C. A. SCHEVON[1], M. R. SPERLING[9], A. SHARAN[10], J. M. STEIN[11], J. JACOBS[2];
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Abstract: From a range of research, the medial-temporal-lobe (MTL) is widely implicated in both memory and spatial navigation. Much of this research has focused on neurons that activate according to an animal's own spatial properties, such as “place cells” in the hippocampus that represent the animal's current location. In addition to representing the current spatial setting, these same MTL structures play an important role in memory, which can also involve remote locations as well as other contextual information. However, the human cellular representations that underlie our ability to form memories that involve remote locations are unclear. To examine this issue we recorded single-neuron activity from neurosurgical patients playing Treasure Hunt (TH), a virtual-reality object--location memory task. We found that the firing rates of many MTL neurons during navigation significantly changed depending on the position of the object the subject was trying to remember, and we refer to these cells as ‘spatial-target cells’. In addition, we observed neurons whose firing rates during navigation were tuned to specific heading directions in the environment, and others that significantly changed with respect to subsequent memory performance. We found that the neurons that encode the spatial target position are largely distinct from those that encode subject position, heading direction, and subsequent memory. Additionally, we verified that the spatial-target cells cannot be explained by possible confounding factors such as the distance to the target and serial position in a trial. We have also begun investigating correlates of eye position during this task. We conclude by discussing how the nature of MTL neuronal coding may vary based on task demands.

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Nanosymposium

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Title: Two senses of direction in human medial temporal lobe

Authors: *L. KUNZ[1], A. BRANDT[1], P. REINACHER[2], B. STARESINA[3], M. TSITSIKLIS[4], J. JACOBS[5], A. SCHULZE-BONHAGE[1];
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Abstract: Neural representations of direction are an essential component of the brain's spatial navigation system, providing essential input to place and grid cells (Moser et al., 2008). Direction information may be stored by means of two opposing yet complementary neural strategies: via local (i.e., single-neuron) and distributed (i.e., network-level) coding. Hence, we set out the current study to examine the question of how direction information is represented in the human brain via single- and multi-unit recordings from the medial temporal lobe of nine epilepsy patients performing a virtual navigation task. We identified a subset of neurons exhibiting directional tuning of their neural firing rates, roughly in line with the firing characteristics of head direction cells in rodents (Taube et al., 1990; Giocomo et al., 2014). These directionally tuned neurons were particularly found in fusiform gyrus and hippocampus. Complementary to this single-neuron code of direction, we found that multivariate spiking activity could be used to predict virtual movement direction within the virtual environment (Quian Quiroga & Panzeri, 2009). In this case, direction information was obtained from populations of neurons, many of which were not or only weakly tuned by direction at the single-cell level. Decoding accuracy was particularly high when combining behavioral and neuronal data from all patients into one "hypersubject" (Meyers et al., 2013), suggesting that distributed coding of direction relied on large neuronal assemblies. Further characterization of neurons positively contributing to decoding accuracy revealed that they were less likely to show theta phase locking as compared to neurons negatively contributing to decoding accuracy. In sum, our results provide evidence for a distributed code of direction in human medial temporal lobe, which orchestrates the sharp directional tuning of highly selective neurons. At a general level, our study provides a reconciling view on local and distributed neural coding in the human brain.

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Nanosymposium

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Title: Decoding mental walkthroughs of spatial memories in an immersive virtual reality environment

Authors: *R. MASIS-OBANDO[1], U. HASSON[1], K. A. NORMAN[1], C. BALDASSANO[2]; [1]Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Psychology, Columbia Univ., New York, NY

Abstract: When recalling autobiographical memories, we can use our semantic knowledge about the spatial and temporal structure of the world (schemas) to help retrieve and elaborate on episodic details. Retrieval of these autobiographical episodes requires that memories be easily accessible (e.g. with cues) and remain stable over time (e.g. from interfering memories). Spatial context serves as one of the most powerful memory cues (Robin et al. 2018). Notably, a brain network engaged by recall of naturalistic episodes contains regions critical for spatial navigation, including Posterior Medial (PM) and Anterior Temporal (AT) network regions that represent context and entities/objects, respectively (Chen et al. 2016, Ranganath and Ritchey 2012). By having subjects first learn a novel spatial environment and then recall information about objects in that environment, we can study how the newly-learned spatial contexts interact with the retrieval of specific episodic content.

Using principles borrowed from the method-of-loci mnemonic technique, commonly known as the "memory palace", we custom-built a virtual reality (VR) environment made up of 23 distinct rooms, which subjects explored using a head-mounted virtual reality display. On day 1 subjects learned the layout of the environment by playing two foraging tasks. In the pre-learning phase on day 2 (1 day later) whole-brain fMRI data were recorded as subjects viewed videos of rooms and random walks through the memory palace; in the learning phase, subjects were taken back to VR to memorize the locations of 23 distinct objects randomly placed within each of the 23 rooms; in the post-learning phase, subjects were scanned as they freely recalled the objects and the rooms in which they appeared, recalled objects along specific paths, and again viewed videos of rooms, objects and random walks through the palace.

Preliminary data show that room and object representations overlap in PM and AT network regions, respectively. Additionally, we used a supervised Hidden Markov Model (HMM) to decode individual subjects' room and object representations as subjects recalled rooms and objects along pre-specified paths, with prediction accuracies reaching as high as 0.70 ($p < 0.05$) for rooms and 0.91 ($p < 0.05$) for objects. High-performing regions overlapped with PM, AT and autobiographical spatial memory regions. Planned analyses of the fMRI data include relating hippocampal activation dynamics to room and object retrieval, and using an unsupervised HMM to track subject-chosen mental trajectories through the environment based on the reactivation of room-specific activity patterns.

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Nanosymposium

272. Basic, Theoretical, and Translational Research on Human Spatial Cognition

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Topic: H.02. Human Cognition and Behavior

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Title: Interactions between hippocampal representations of goals and decision points

Authors: *I. K. BRUNEC[1,2], J. ROBIN[2], J. D. OZUBKO[3], M. D. BARENSE[1,2], M. MOSCOVITCH[1,2];
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Abstract: During large-scale navigation, turns along travelled routes provide crucial junctions for decision-making and enable navigational planning. Rodent neurophysiology work provides evidence of forward 'sweeps' in hippocampal firing at decision points, indicating that junctions during navigation promote the sampling of potential future routes. Converging human neuroimaging findings show that hippocampal activity during route planning and at decision points reflects the simulation of future navigational choices. It is not known, however, whether and how the magnitude of local future planning relates to global goal representations.
To investigate how moment-to-moment fluctuations during navigation relate to goal representations, we used a sliding window representational similarity analysis, where the voxelwise pattern at each TR was correlated to the subsequent TR. Local sampling at each turn on a route was defined as the degree of signal carry-over from pre-turn to post-turn timepoints (TRs). To obtain a measure of global goal representation at each timepoint, we correlated every TR on a route with the final (goal) TR. We then extracted only the decision points on each route and related the extent of local sampling at each decision point to the degree of goal similarity at the same timepoint. We implemented this approach on fMRI data from 19 participants navigating in a familiar virtual environment. Participants navigated an average of 70.2 routes within a virtualized version of the University of Toronto campus, built using Google Street View images.
A higher degree of local sampling might relate to a stronger goal-directed representation, if what is represented at the decision point is the final goal on the route. Alternatively, a higher degree of local sampling may relate to the final goal representation negatively, as it may narrow the representational scope to the immediate surroundings and inhibit global goal representations. Our results provide evidence for the latter, as higher local sampling at decision points was related to lower goal similarity. Importantly, however, while higher local sampling was related to lower goal similarity early in each route, the pattern reversed towards the end of the route, where

higher local sampling was related to stronger goal representations. Together, these data provide evidence for the importance of decision points in balancing immediate future planning and global goal representations during navigation even in highly familiar environments.

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Title: Deforming the metric of cognitive maps distorts memory

Authors: *J. L. S. BELLMUND[1,2,3], W. DE COTHI[4], T. A. RUITER[3,5], M. NAU[3], C. BARRY[4], C. F. DOELLER[1,3];
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Abstract: Environmental boundaries anchor cognitive maps. However, trapezoidal boundary geometry distorts the regular firing patterns of entorhinal grid cells thought to provide a metric for cognitive maps. Here, we test the impact of trapezoidal boundary geometry on human spatial memory using highly immersive virtual reality. Consistent with reduced regularity of grid patterns in rodents and in the eigenvectors of the successor representation, human positional memory was degraded in a trapezoid compared to a square control environment; an effect particularly pronounced in the trapezoid's narrow part. Congruent with changes in the spatial frequency of eigenvector grid patterns, distance estimates between remembered positions were persistently biased; resulting in distorted memory maps which explained behavior better than objective maps. Our findings demonstrate that environmental geometry interacts with human spatial memory similarly to how it affects rodent grid cells - thus strengthening the putative link between grid cells and behavior along with cognitive functions beyond navigation.

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Nanosymposium

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Title: Predicting future sequence and distance to goal with multi-scale successor representations

Authors: M. W. HOWARD[1], ***I. MOMENNEJAD**[2];
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Abstract: The successor representation (SR) is a candidate principle for generalization in reinforcement learning, computational accounts of memory, and the structure of neural representations in the hippocampus. Given a sequence of states, the SR learns a predictive representation for every given state that encodes how often, on average, each upcoming state is expected to be visited, even if it is multiple steps ahead. A discount or scale parameter determines how many steps into the future SR's generalizations reach, enabling rapid value computation, subgoal discovery, and flexible decision-making in large trees. However, SR with a single scale discards information for predicting both the sequential order of and the distance between states, which are common problems in navigation for animals and artificial agents. Here we propose a solution: an ensemble of SRs with multiple scales. We show that a set of SRs with a spectrum of discount rates encodes the Laplace transform of the future. Building on this insight, we show that taking derivative of multi-scale SR with respect to the discount rate approximates the inverse Laplace transform. This representation reconstructs both (a) the sequence of expected future states and (b) estimate distance to goal. The distance to goal estimation qualitatively fits single neuron results from the medial temporal lobe neurons of bats (Sarel et al. 2017), rodents (Gauthier and Tank, 2017), and humans (Qasim et al. 2018). The derivative of multi-SR---i.e., the inverse Laplace transform---can be computed linearly and is biological plausible. In short, multi-scale SR and its derivative allow the reconstruction of future sequences and estimation of distance to goals at different scales. Coupled with recent evidence that the MTL contains the Laplace transform of the past (Tsao, et al., 2018; Bright, Meister, et al., 2019) and the Laplace transform of spatial variables (Howard, et al., 2014), this framework could lead to a common principle for how the medial temporal lobe supports both map-based and vector-based navigation.

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Nanosymposium

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Title: The role of the pre-commissural fornix in an extended neuroanatomical network for goal-directed navigation

Authors: *M. POSTANS[1], A. N. WILLIAMS[1], M. STEFANI[1], R. LISSAMAN[1], B. S. KOLARIK[2], A. P. YONELINAS[3], A. D. EKSTROM[4], A. D. LAWRENCE[1], J. ZHANG[1], K. S. GRAHAM[1], C. J. HODGETTS[1];
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Abstract: While the hippocampus has been a key focus of spatial navigation research, the prefrontal cortex, septum and striatum are also thought to be critical for learning to navigate to specific spatial locations. This is most likely facilitated via the pre-commissural fornix. By contrast, animal lesion studies suggest that the descending component of the post-commissural fornix, which links the hippocampus to the mammillary bodies, is not necessary for successful navigational learning (Vann et al., 2011). Here, we used white matter tractography to investigate potential differential contributions of the pre-commissural versus descending post-commissural fornix in goal-directed navigational learning, assessed using a virtual Morris Water Maze task. Previous studies using similar navigational paradigms have relied on behavioural performance metrics that contain no information about the spatial distribution of subjects' search trajectories (e.g., escape latency), which can obscure subtle differences in subjects' spatial localisation ability. By contrast, we used curve-fitting techniques to derive a single index of participants' navigational learning rate from a trial-wise measure of cumulative proximity to a target location (target-proximity sampled over 1 second intervals and then summed), a measure reflecting differences in participants' spatial search error (Gallagher et al. 1993). We then asked how inter-individual variation in these navigational measures were associated with individual variation in diffusion MRI measures of pre- and post-commissural white matter microstructure (Fractional Anisotropy, FA, and Mean Diffusivity, MD), in a group of 33 healthy individuals (18 females;

mean age=24 years, SD=3.5 years). Navigational learning rate measure was negatively correlated with pre-commissural fornix FA (r = -0.449, p = 0.014), indicating that individuals with higher pre-commissural fornix FA made greater cross-trial improvements in their target location localisation. This structure-behaviour association was not reproduced in the descending post-commissural fornix (r = 0.105, p = 0.313), and these correlations were significantly different (z = -2.214, p = 0.013). Further, the association between pre-commissural fornix FA and participants' navigational learning rate remained significant when controlling for hippocampal volume (r = -0.451, p = 0.015). These findings are consistent with emerging models proposing a spatially distributed neuroanatomical network for human goal-directed navigation, and highlight that communication across this extended functional network is mediated in part by the pre-commissural fornix.

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Title: Developmental differences in optimal locomotion methods for spatial updating in virtual reality

Authors: *E. BARHORST-CATES, S. CREEM-REGEHR, J. STEFANUCCI;
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Abstract: Spatial updating is the ability to maintain knowledge of one's spatial position in the environment and in humans, typically involves both visual and motor cues for self-motion. Previous research has shown developmental differences in sensorimotor dependency for spatial cognition. Some studies show greater visual dependency in children compared to adults while others show greater motor dependency in children, depending on the task. The current study aimed to test differences in visual and motor dependency in a spatial updating task with children age 10-12 and young adults using immersive virtual reality. 30 Children and 40 adults completed a triangle completion task in a full-cue virtual room using three locomotion methods that varied the presence of visual and body-based information for translation: Walking (both body-based and visual), Joystick (visual only), and Teleporting (neither body-based nor visual). Real rotations

were included in all conditions. Participants also completed measures of balance ability to assess the effects of motor control on spatial updating performance. We predicted that adults would outperform children in all conditions and that all participants would perform best in the Walking condition, followed by Joystick, followed by Teleporting, because of the subsequent reduction in available cues in each condition, respectively. Surprisingly, adults were equally accurate in both Walking and Joystick, and children were most accurate in Joystick, followed by Walking. Teleporting resulted in the worst performance for both groups. Adults outperformed children in all conditions, and children were more negatively impaired than adults when visual information was taken away (in Teleporting compared to Joystick). There were clear improvements in all conditions with age, both within children and across children and adults. Finally, better balance ability (longer time balancing on one foot) both with and without vision led to lower Teleporting error. These data suggest that adults may be more flexible in using either visual or body-based information for self-motion, but children are most accurate with and more dependent on visual information. Balance ability plays a role in difficult spatial updating tasks, suggesting that physical stability may facilitate navigation performance. Taken together, these results point to the importance of considering developmental differences in sensorimotor dependence for human spatial updating and navigation. This research also has practical implications for using virtual reality as a research and rehabilitation technique in psychology and neuroscience.

Disclosures: E. Barhorst-Cates: None. **S. Creem-Regehr:** None. **J. Stefanucci:** None.

Nanosymposium

272. Basic, Theoretical, and Translational Research on Human Spatial Cognition

Location: Room S405

Time: Monday, October 21, 2019, 8:00 AM - 11:30 AM

Presentation Number: 272.13

Topic: H.02. Human Cognition and Behavior

Support: Korea Institute of Science and Technology(KAIST) grant (Deconstructing meditation into its neurocognitive components)
HYUNDAI NGV grant
Institute of Information & Communications Technology Planning & Evaluation(IITP) grant funded by the Korea government (MSIT) (No.2019-0-01371, Development of brain-inspired AI with human-like intelligence)

Title: Neural representation of episodic memory components in the prefrontal cortex measured by fNIRS

Authors: *J. SHIN[1], S. LEE[2];
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Abstract: Episodic memory (EM) is a key cognitive function that enables us to recall details of past experiences, including content ("what"), space ("where"), and time ("when"). While humans can effortlessly remember a spatiotemporally continuous episode, a detailed understanding of the neural mechanisms underlying temporal binding of memory components is still unclear. The hippocampus is widely known for its role in spatiotemporal representations including EM, but the prefrontal cortex (PFC) also plays an important role and is of interest due to its accessibility using a wide range of methodologies for measuring and modulating neural activity. In this study, we used a high-density portable functional infrared spectroscopy (fNIRS) system to investigate PFC activity in an EM task that required the temporal binding of "what" and "where" information.
Subjects (n=15) were asked to perform a computer-based EM task in which they were asked to place a subset of available objects in a subset of available locations in a specific temporal order (encoding) and, then, re-enact that entire sequence after a delay (retrieval). We dissociated EM temporal binding into three trial types: (1) what-when binding, (2) where-when binding and (3) what-where-when binding (full EM). In the full EM trial, subjects successfully recognized objects and locations (what and where) but made more errors when recalling their temporal order. In the componential trials (what-when or where-when binding), however, behavioral performance in both recognition and temporal binding were at ceiling.
Multi-class SVM based on multi-depth NIRS channels could classify each trial type and memory process (demo/encoding/retrieval) with an accuracy of more than 80%. Overall PFC activation was greater in the full EM trial than the componential conditions during encoding and retrieval period (what: $t(17)=2.38$, $p=.023$ / where: $t(17)=3.94$, $p=.001$), particularly in the right PFC (what: $t(17)=2.84$, $p=.011$/ where: $t(17)=2.87$, $p=.011$). Interestingly, full EM showed a tendency toward higher activation than both of the componential conditions in dorsolateral PFC (what: $t(17) = 1.92$, $p=.071$ / where: $t(17)=2.85$, $p=.011$), but higher activation during full EM in ventrolateral PFC was only observed in comparison with what-when condition, not with the where-when condition. (what: $t(17)=2.15$, $p=.046$ / where: $t(17)=0.96$, $p=.35$) Our study provides insight into how PFC activity varies with temporally-binded memory components in episodic memory. Such knowledge could be applied to the assessment of memory-related neural activity in a wide range of experimental and clinical settings, using portable fNIRS systems.

Disclosures: J. Shin: None. **S. Lee:** None.

Nanosymposium

272. Basic, Theoretical, and Translational Research on Human Spatial Cognition

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Presentation Number: 272.14

Topic: H.02. Human Cognition and Behavior

Support: DFG SFB1280

DFG SFB874

Title: Selective impairment of path integration in adults at genetic risk for Alzheimer's disease

Authors: *A. BIERBRAUER[1], L. KUNZ[3], C. A. GOMEZ[1], M. LUHMANN[2], L. DEUKER[1], S. GETZMANN[4], E. WASCHER[4], P. GAJEWSKI[4], M. FERNANDEZ-ALVAREZ[5], M. ATIENZA[5], D. M. CAMMISULI[6], F. BONATTI[6], C. PRUNETI[6], A. PERCESEPE[6], Y. BELLAALI[7], B. HANSEEUW[7], B. A. STRANGE[8], J. L. CANTERO[5], N. AXMACHER[1]; [1]Dept. of Neuropsychology, Inst. of Cognitive Neuroscience, Fac. of Psychology, [2]Fac. of Psychology, Ruhr Univ. Bochum, Bochum, Germany; [3]Dept. of Epileptology, Univ. of Freiburg, Freiburg, Germany; [4]Leibniz Res. Ctr. for Working Envrn. and Human Factors, Tech. Univ. of Dortmund, Dortmund, Germany; [5]Lab. of Functional Neurosci., CIBERNED, Pablo de Olavide Univ., Seville, Spain; [6]Dept. of Med. and Surgery, Lab. of Clin. Psychology, Psychophysiology and Clin. Neuropsychology, Univ. of Parma, Parma, Italy; [7]Dept. of Neurol., Cliniques Universitaires Saint-Luc, Inst. of Neuroscience, Univ. Catholique de Louvain, Brussels, Belgium; [8]Dept. of Neuroimaging, Alzheimer's Dis. Res. Centre, Reina Sofia– CIEN Fndn., Madrid, Spain

Abstract: Alzheimer's disease (AD) is the most common form of dementia and manifests with memory loss and spatial disorientation. Currently, no causal therapies for AD are available, potentially because otherwise effective drugs are applied too late - rendering the preclinical identification of people at risk at high importance. Neurodegeneration in preclinical AD starts in entorhinal cortex and hippocampus, making it likely that local neural substrates of spatial navigation, particularly grid cells, are impaired in early disease stages. Indeed, previous studies showed impaired fMRI grid representations in young adults at genetic risk for AD (*APOE* E4-carriers). Since grid cells presumably support path integration, we hypothesized that path integration is selectively impaired in adults at genetic risk for AD, in particular when no salient navigational cues are available to stabilize grid representations. Therefore, we applied a novel virtual reality paradigm in n=267 genotyped participants across five European sites (103 males; mean age: 37.72; range: 18 - 75) and in a parallel fMRI task (n=35; 17 males; mean age: 24.97; range: 19 - 35). We demonstrate a selective deterioration of path integration performance in *APOE* E4-carriers in the absence of salient local or distal navigational cues. By contrast, both genetic subgroups performed equally well in virtual environments with a surrounding boundary or a local landmark. Detailed analyses revealed distinct dependencies of risk and control participants on different aspects of the path integration task, generally suggesting that *APOE* E4-carriers rely more strongly on spatial information derived from environmental navigational cues. A separate fMRI study unveiled the neural correlates of our path integration task. In sum, our results provide evidence for dysfunctional changes in path integration behavior in adults at genetic risk for AD, decades before potential disease onset.

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Nanosymposium

273. Learning and Decision-Making

Location: Room S106

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 273.01

Topic: H.02. Human Cognition and Behavior

Title: A psychophysical task to quantify and operationalize subjectively perceived boredom

Authors: *O. DAN[1], J. SEILER[2], S. RUMPEL[2], O. TÜSCHER[3], Y. LOEWENSTEIN[4]; [1]Cognitive Sci., The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Johannes Gutenberg Univ. Mainz, Mainz, Germany; [3]Univ. Med. Ctr. Johannes Gutenberg-University, Clin. for Psychiatry and Psychotherapy, Mainz, Germany; [4]Hebrew Univ., Jerusalem, Israel

Abstract: Boredom, as often experienced in everyday life, has been defined as an aversive mental state that is associated to the disability to engage in satisfying activity (Eastwood et al., 2012) and was implicated in several clinical conditions including ADHD and depression. However, research on boredom is still scarce and current measures of boredom rely on subjective self-report questionnaires. Here, we developed a psychophysical task in humans that allows the quantification and operationalization of boredom. We used a two-choice preference task, with the two alternatives being associated with different sensory stimuli, either monotonous or variable. The stimuli used were either visual stimuli of images of daily-life objects (BOSS by Brodeur et al., 2010) or auditory stimuli consisting of single spoken German words. We analyzed how boredom, as measured in standard self-reports, correlates with an avoidance of the monotonous sensory stimulus. We observed a choice bias towards the variable over the monotonous alternative that was significantly correlated to the self-reported level of state boredom (MSBS by Fahlman et al., 2013; n=102 healthy subjects, $R=0.30$, $p<0.01$). Interestingly, this effect was comparable between experiments using visual and auditory stimuli, consistent with the idea that boredom is independent of a specific sensory modality. We next quantified the choice bias over a range of varying degrees of monotony and variability by controlling the size of the stimulus libraries that were associated with each of the two alternatives. Together, we established an objective behavioral task that captures aspects of subjectively reported state boredom in humans. The simplicity of this task will enable us to eventually study boredom in non-human models, in which the neural mechanisms are experimentally more accessible.

Disclosures: O. Dan: None. **J. Seiler:** None. **S. Rumpel:** None. **O. Tüscher:** None. **Y. Loewenstein:** None.

Nanosymposium

273. Learning and Decision-Making

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Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 273.02

Topic: H.02. Human Cognition and Behavior

Support: Northern Norway Regional Health Authority (grant no. PFP1237-15)

Title: Experimentally induced helplessness in healthy humans modulates cognitive control over Pavlovian bias in action selection

Authors: G. CSIFCSÁK, E. MELSÆTER, **M. MITTNER**;
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Abstract: Learned helplessness (LH) is a central concept in the psychopathology of depression and many anxiety-related disorders. Recently it was suggested that LH might be dominated by strong Pavlovian influences over action selection, manifesting in increased tendency to remain passive when facing potential threat (Maier and Seligman, 2016). This study directly tested whether a behavioral manipulation designed to induce LH ("yoking") in a reinforcement learning task is associated with enhanced Pavlovian bias, weaker cognitive control and impaired feedback processing in healthy female and male human participants. Using model-free and model-based analysis of behavioral data and specific electroencephalographic signals, frontal midline theta power during decision-making and event-related potentials reflecting outcome evaluation, we found evidence for this hypothesis both in the loss and reward domains. Our findings support the view that LH might not be learned, but rather, be dominated by innate behavioral response tendencies to emotionally salient stimuli when executive control is weak. However, we also show that yoking is not necessarily maladaptive, as it prevents the overgeneralization of decision-making strategies and the excessive recruitment of cognitive control in trials when Pavlovian bias is actually beneficial. These results might contribute to a better understanding of the behavioral and neural features of helplessness and maladaptive cognitive control across in a range of psychopathologies.

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Nanosymposium

273. Learning and Decision-Making

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Presentation Number: 273.03

Topic: H.02. Human Cognition and Behavior

Support: DFG Emmy-Noether Programm PE 1627/5-1

Title: Dopaminergic manipulation of the explore/exploit trade-off in human decision-making

Authors: K. CHAKROUN[1], ***D. MATHAR**[3], A. WIEHLER[4,1], F. GANZER[2], J. PETERS[3]; [1]Dept. of Systems Neurosci., [2]German Ctr. for Addiction Res. in Childhood and Adolescence, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany, Germany; [3]Dept. of Psychology, Biol. Psychology, Univ. of Cologne, Cologne, Germany; [4]Motivation Brain Behavior, ICM - Hop. Pitie Salpetriere, Paris, France

Abstract: Introduction: Dopamine (DA) neurotransmission has been hypothesized to play a key role in the balance of exploration and exploitation (Frank et al., 2009; Beeler, 2012). Computational modeling can be used to examine the latent processes supporting exploration behavior (Daw et al., 2006; Gershman 2018). Here, we used a combination of pharmacological intervention, computational modeling and fMRI to directly examine the effect of dopaminergic modulation on the explore/exploit trade-off in humans.
Methods: 31 healthy male subjects (19 to 35 years) participated in a double-blind, placebo-controlled, within-subjects study consisting of three separate fMRI sessions. During MRI participants performed a restless four-armed bandit task (Daw et al., 2006) under three drug conditions: 150mg L-dopa (Madopar), 2mg haloperidol, and placebo (maize starch). Task performance was modeled with six different computational learning models within a hierarchical Bayesian modeling scheme. Model selection was achieved via Bayesian leave-one-out cross-validation (Vehtari, Gelman, & Gabry, 2017). Behavior was best accounted for by a model including terms for perseveration behavior and uncertainty-driven exploration (*exploration bonus*).
Results: Uncertainty-driven exploration was robustly associated with a change in exploration behavior: the group-level posterior distribution for the exploration bonus parameter was substantially reduced under L-DOPA compared to both haloperidol and placebo. Across all drug conditions, exploratory choices were associated with greater activation in frontopolar cortex (FPC; -42, 27, 27 mm; z=6.07; 39, 34, 28 mm; z=7.56), and in dorsal anterior cingulate cortex (dACC; 8, 12, 45 mm; z=8.47) among others. We observed no general drug-related differences in activation during task-performance. However, model-based fMRI analysis revealed that neural tracking of model-based uncertainty in posterior insula (-34, -20, 8mm; z=5.05), and, to a lesser degree ($p<.001$ uncorrected) in dACC (-2, 36, 33mm; z=3.32; 4, 14, 28mm; z=3.41) was attenuated under L-dopa compared to placebo.
Conclusion: L-dopa attenuated uncertainty-driven exploration in healthy participants. Model-based fMRI analysis indicated that L-dopa might have delayed the time point at which directed exploration was triggered in response to accumulating uncertainty.

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Nanosymposium

273. Learning and Decision-Making

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Presentation Number: 273.04

Topic: H.02. Human Cognition and Behavior

Support: SNSF Grant 100014_153616

Title: Violations of economic rationality in reinforcement learning are driven by a saliency-dependent reward prediction error signal in the ventral striatum

Authors: *S. GLUTH[1], M. SPEKTOR[2], J. RIESKAMP[1];
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Abstract: When making decisions between more than two choice options humans and other animals frequently violate the independence principle of rational choice theory. According to this principle, the relative choice probability between two options should not depend on any other option. In our previous work (Spektor et al., 2019, Psychological Review), we showed that these violations can also occur in reinforcement learning (RL) tasks. We developed a novel RL model, the Accentuation-of-Differences (AOD) model, which proposes a saliency-based distortion of feedback processing. More specifically, the reward prediction error (RPE) of options with very distinct outcomes is assumed to be biased in the positive direction. In the current study, we set out to test this proposal on the neural level by investigating the fMRI-BOLD signal of the RPE in the ventral striatum. We tested N = 40 participants who completed two sessions of an RL task with three choice options each (A, B, C; B, C, D). Reward contingencies for two of the three choice options (B and C) were equal across sessions, which allowed us to test for violations of the independence principle. The third option (A in session 1 and D in session 2) was specified such that the AOD model would predict a preference for C over B in session 1 and vice versa in session 2. fMRI data was acquired on a 3T MR scanner. Analysis of the choice behavior provided very strong evidence for the predicted independence violation: The relative choice share of the target option (C in session 1, B in session 2) was .71, which was significantly larger than .50 ($t(39) = 6.28$, $p < .001$, $d = 0.99$). Similarly, the AOD model provided a better account of the choice data compared to a standard RL model and a risk-sensitive RL model. Model-based fMRI data analysis revealed a significant AOD-based RPE signal in the ventral striatum, even after controlling for the reward signal itself ($Z = 5.42$, p(whole-brain corrected) = .005). Critically, a Bayesian model comparison of the brain data showed that the AOD model provided a better account of the RPE signal in the ventral striatum than the competing RL models. In conclusion, our study provides further evidence for violations of the independence principle in RL decisions and elucidates the underlying neural mechanism. Feedback processing in the reward system of the brain is influenced by the distinctiveness of outcomes such that particularly salient options are preferred.

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Nanosymposium

273. Learning and Decision-Making

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Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 273.05

Topic: H.02. Human Cognition and Behavior

Support: Fondecyt 1180932
Anillo ACT1414

Title: Human anterior insula encodes prediction error through amplitude modulation of beta oscillations

Authors: *T. OSSANDON[1], P. FUENTEALBA[1], J.-P. LACHAUX[2], P. BILLEKE[3];
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Abstract: Adaptive behavior requires the comparison of outcome predictions with actual outcomes. This comparison is evaluated in terms of prediction error, which is computed by a distributed brain network comprising the medial prefrontal cortex (mPFC) and the anterior insular cortex (AIC). These areas are the main cortical target of mesolimbic dopaminergic neurons signaling prediction error during reinforcement learning. Despite being consistently co-activated during performance monitoring, the precise neuronal computations in each region and their interactions remain elusive. In order to assess the neural mechanism by which AIC processes performance feedback, we recorded AIC electrophysiological activity from 21 neurosurgical epileptic patients with intracerebral deep electrodes for presurgical evaluation while they carried out various cognitive tasks with continuous performance feedback. We tested the hypothesis that the AIC encodes performance feedback in order to adapt ongoing behavior to environmental conditions. In particular, we predicted that the electrophysiological activity of the AIC is modulated by prediction errors, and that it exerts a causal influence on other cortical areas related to feedback processing and reward-based learning, such as the medial prefrontal region. We found that the AIC encodes unsigned prediction error through specific amplitude modulation of beta oscillations. Furthermore, the valence of feedback was encoded by delta waves phase-modulating the power of beta oscillations. Finally, connectivity and causal analysis showed that beta oscillations relay prediction error signals to mPFC. These results reveal that structured oscillatory activity in the anterior Insula encodes prediction error and performance feedback valence, thus coordinating brain circuits related to reward-based learning.

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Nanosymposium

273. Learning and Decision-Making

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Presentation Number: 273.06

Topic: H.02. Human Cognition and Behavior

Support: CRCNS R01MH115557-01.

Title: Hierarchical inference interactions in dynamic environments

Authors: *T. L. EISSA[1], N. W. BARENDREGT[1], J. I. GOLD[2], K. JOSIC[3], Z. P. KILPATRICK[1];
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Abstract: In a constantly changing world, accurate decisions require flexible evidence accumulation where old information is discounted at a rate adapted to the frequency of environmental changes. However, sometimes humans and other animals must simultaneously infer the state of the environment and its volatility (hazard rate) in order to appropriately discount evidence at a rate matched to the environmental timescale. To probe how these inference processes interact when performed hierarchically, we develop and analyze a model of an ideal observer who makes noisy measurements of a two-state environment with an initially unknown hazard rate that is either high (changes happen often) or low (changes are rare). Using log-likelihood ratios (LLRs) of the state and hazard rate, we track how the observer's inferences about the environment evolve over time. We find that hazard rate accuracy builds up slowly, with information at change points (CPs) providing evidence for the high rate and the time between CPs building evidence for the low rate. In contrast, state accuracy drops immediately after CPs and recovers at a rate dependent on the observer's estimated hazard rate. Quantifying this recovery rate, we find that the recovery rate is correlated with a tradeoff in overall state accuracy, with lower accuracy associated with faster recovery rates, and that the speed of post-CP recovery shifts over trial duration as the true hazard rate is learned. The effect of the observer's hazard belief on the recovery rate can therefore be attributed to hierarchical interaction between the two inference processes. Notably, however, we also identify situations within the normative model in which the hazard rate is not correctly learned. We hypothesize that this discrepancy is caused by a hierarchical confirmation bias and examine perturbations of the normative model and priors that can exacerbate this bias. We also determine whether this result is a generalized phenomenon in interacting inference models. Thus, we conclude that there are distinct regimes where hazard rate inference influences state inference but also that hazard rate inference appears fragile and can be biased against inferring the true environmental hazard rate. Identifying the regimes and perturbations that lead to hierarchical inference and hierarchical bias respectively is therefore critical to decision-making task design and the interpretation of subject responses.

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Nanosymposium

273. Learning and Decision-Making

Location: Room S106

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Presentation Number: 273.07

Topic: H.02. Human Cognition and Behavior

Title: A computational window into the problem with organoids: Approaching minimal substrates for consciousness

Authors: *E. L. OHAYON[1,2], P. W. TSANG[2,3], A. LAM[1,2,4];
[1]Green Neurosci. Lab., Neurolinx Res. Inst., San Diego, CA; [2]Green Neurosci. Lab., Inst. for Green and Open Sci., Toronto, ON, Canada; [3]Ontario Inst. for Studies in Educ., Univ. of Toronto, Toronto, ON, Canada; [4]Physicians Committee for Responsible Med., Washington DC, DC

Abstract: A central question in neuroscience relates to the underlying mechanisms and minimal conditions for consciousness. There are at least five domains that can help anchor this question when studying the brain: [1] compositional (e.g., atomic, molecular), [2] causal (e.g., genetic, evolutionary), [3] anatomical (e.g., cellular, network geometry, brain regions), [4] physiological (e.g., cellular, network, whole brain activity), and [5] behavioral (e.g., embodied, virtual). Here we present several computational network models and accompanying methods for analyzing dynamics that may help identify the encroachment toward functional and possibly sentient activity. As a test case, we consider these features in stem cell cultures. Artificial genetic modification notwithstanding, the compositional and causal features in these cultures are -- by design -- often very similar to naturally occurring neural substrates. Recent developments in organoid research also entail that the anatomical substrates are now approaching local network organization and larger structures found in sentient animals. As such, the assessment of the physiological activity has become critical. Assessment informed by the models and associated dynamics suggests that current organoid research is perilously close to crossing this ethical Rubicon and may have already done so. Despite the field's perception that the complexity and diversity of cellular elements *in vivo* remains unmatched by today's organoids, current cultures are already isomorphic to sentient brain structure and activity in critical domains and so may be capable of supporting sentient activity and behavior. Although stem cell research holds much promise in moving toward more precise and ethical human-based personalized medicine, the implications of the above observations indicate that there is an urgent need for identifying methods and criteria for sentience that can help set ethical rules for research conduct. It is

important to note that the observations in this computational study point at minimal guidelines and undoubtedly would fail to identify alternate forms of sentience.

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Nanosymposium

273. Learning and Decision-Making

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Support: NIMH Grant 1R01MH109954-01

Title: Spatiotemporal dynamics of arithmetic processing in the human brain

Authors: *P. PINHEIRO-CHAGAS, C. SAVA-SEGAL, S. AKKOL, A. L. DAITCH, J. PARVIZI;
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Abstract: Evidence from neuroimaging studies have provided a static and coarse functional map of arithmetic processing in the brain, characterized by a network of regions that overlap with the intrinsic frontoparietal and dorsal attention networks, and largely dissociate from the language network. However, the precise anatomical location, temporal dynamics and specific roles of each hub, as well as how they collaboratively work to perform a calculation is still poorly understood. In the present study, we recorded intracranial electroencephalography (iEEG) signals from 100 subjects (58 implanted with grids and 42 with depth electrodes; total of 9,010 recording sites), while they performed a variety of arithmetic tasks from basic number recognition to arithmetic verification. Corroborating previous fMRI studies, results showed a distinct network of regions selectively activated (indexed by high frequency broadband activity (HFB): 70-170Hz) during arithmetic, that included four main hubs: posterior inferior temporal gyrus (pITG), intraparietal sulcus (IPS), superior parietal lobule (SPL) and dorsolateral prefrontal cortex (DLPFC), which dissociated from canonical regions selectively activated during the control conditions: memory retrieval and sentence reading. Moreover, responses to calculations were generally format independent (i.e. comparable for Arabic numbers and number words), suggesting that number manipulation is performed at an abstract level. Next, a response onset latency map revealed a cascade of partially overlapping activations from early visual areas to pITG, followed by IPS/SPL, then by DLPFC and lastly by motor regions, associated with the response. Finally, functional connectivity (FC) analysis showed a high degree of connectivity between the main arithmetic hubs during task and also during rest, suggesting that these regions are part of the same intrinsic network. Moreover, the degree of FC between the hubs, specially between the IPS and DLPFC, accurately predicted response times at the single-trial level. Therefore, our results

provide a first detailed and large-scale, anatomical, temporal and functional map of arithmetic processing in the brain.

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Nanosymposium

273. Learning and Decision-Making

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Presentation Number: 273.09

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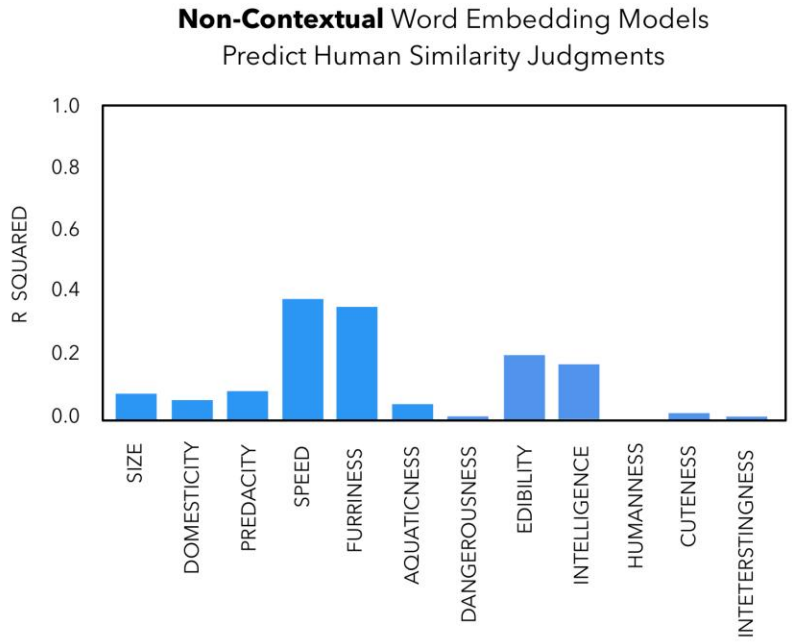
Support: NSF REU

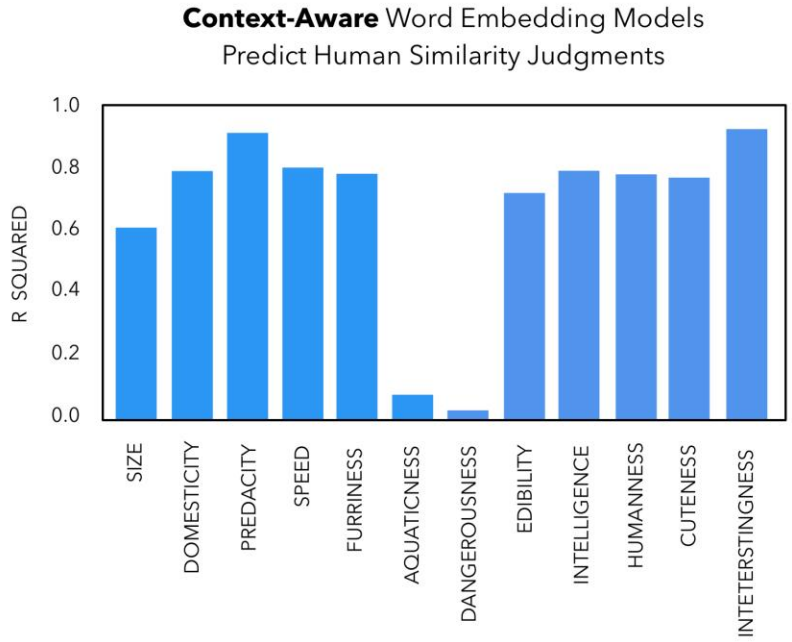
Title: Context-aware word embedding models significantly improve prediction of human conceptual similarity relationships

Authors: *T. GIALLANZA[1], M. IORDAN[2], C. ELLIS[3], J. D. COHEN[2];
[1]Lyle Sch. of Engin., Southern Methodist Univ., Dallas, TX; [2]Princeton Neurosci. Inst. & Psychology Dept., Princeton Univ., Princeton, NJ; [3]Yale Univ., New Haven, CT

Abstract: High-dimensional word embedding models (Word2Vec, Mikolov et al. 2013; GloVe, Pennington et al. 2014) have emerged as popular methods for studying implicit relationships between semantic concepts using lexical co-occurrences in large-scale natural language corpora (e.g., Wikipedia). However, despite their richness, such models have only a limited ability to predict human similarity judgments between complex, real-world objects (e.g., bear and tiger) (Grand et al. 2018). We hypothesize that this gap may be partially due to attentional biases that influence human similarity judgments, and that are not accounted for in general, large-scale corpora typically used to construct such models. More specifically, large corpora merge together materials generated in many different contexts, across which relationships between concepts are highly variable (‘bear’ and ‘bull’ are highly co-occurring in financial publications, but less so in nature-centric articles). We predict that by constructing word embedding models from corpora that reflect specific contexts (e.g., nature-related sources), it may be possible to better capture attentional influences that bias similarity judgments. To test this hypothesis, we collected human similarity judgments between all pairs of 10 animals (e.g., bear) along 12 separate features (e.g., size) and compared this similarity structure to those resulting from Word2Vec models trained on non-contextual (Wikipedia, unconstrained) and context-aware (Wikipedia restricted to nature-related articles) corpora. We found that context-aware models significantly outperformed non-contextual models at recovering similarity relationships that match those of human observers along 10 out of the 12 features we considered. This suggests that the context of training corpora used to derive embedding models exerts a strong influence on the ability of those models to

capture human-assessed relationships between concepts. Our findings open the possibility for significant improvements in the usability of word embedding models in studying human behavior.





Disclosures: **T. Giallanza:** None. **M. Iordan:** None. **C. Ellis:** None. **J.D. Cohen:** None.

Nanosymposium

273. Learning and Decision-Making

Location: Room S106

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 273.10

Topic: H.02. Human Cognition and Behavior

Support: R01DA038063
F32MH110135
NARSAD Young Investigator Grant (Brain & Behavior Foundation

Title: Self control costs show sensitivity to temptation intensity, risk and uncertainty

Authors: *C. M. RAIO[1], L. LEONE[2], P. W. GLIMCHER[1];
[1]Neurosci. Inst., New York Univ., New York, NY; [2]Psychology, Fordham Univ., New York, NY

Abstract: A growing body of research suggests that choosing tempting rewards that do not align with ones broader goals ('self-control failure') may emerge from a decision-making process that weighs the costs of exerting cognitively demanding control against its perceived benefits. We recently found that the subjective cost of exercising self-control can be quantified in humans and that these costs are highly sensitive to changes in affective and motivational states. Specifically, we demonstrated that individuals are willing to incur monetary costs to adopt prospective strategies to restrict access to temptation, offering a quantifiable index of individuals' aversion to deploying effortful behavioral control in the manner predicted by economic models of this process. Here, we aimed to extend this work by testing (1) how self-control costs scale with increasing levels of temptation and (2) whether control costs are sensitive to risk and uncertainty. In Study 1 (n=40), healthy, hungry dieters were endowed with $10 and reported their willingness-to-pay on each trial to avoid spending varying amounts of time with food rewards that ranged in temptation level. One bid was randomly selected at the end and realized using a standard economic auction procedure (Becker-DeGroot-Marschak method). We found that variations in temptation level elicited different self-control costs as measured by bids, tracking the full spectrum of these costs in a manner predicted by economic theory. In Study 2 (n=25), dieters made a series of incentive-compatible binary choices between spending a predictable amount of time with a tempting food reward (certain option) or a lottery option, for which they could be required to spend a greater amount of time with this food (5-60 minutes), or no time at all (0 minutes). Critically, the probability of each option was either stated explicitly (risk) or with some degree of uncertainty (ambiguity). Results revealed a marked preference for certainty, such that participants were less likely to choose risky and ambiguous lottery choices where the level of self-control required on a given trial was not certain. Further, participants accepted fewer lottery choices when the probabilities of each option were ambiguous as opposed to risky. Thus, participants are averse to choice environments in which they cannot fully predict how cognitively costly self-control will be - showing both risk and ambiguity aversion the domain of

self-control. Collectively, these findings suggest that the cost of self-control is shaped by preferences for risk and ambiguity and is sensitive to increases in effort imposed by temptation.

Disclosures: C.M. Raio: None. **P.W. Glimcher:** None. **L. Leone:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.01

Topic: H.02. Human Cognition and Behavior

Title: Shared time-varying functional network architecture across movie-watching and rest

Authors: *R. BETZEL[1], L. BYRGE[2], F. ZAMANI ESFAHLANI[1], D. P. KENNEDY[2];
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Abstract: Cognitive processes are underpinned by coordinated brain activity. These coordination patterns can be modeled as networks of nodes and edges, which represent neural elements and their functional connections (FC). The organization of FC is not fixed across time; rather, FC must flexibly reconfigure in response to external stimuli and to meet ongoing cognitive demands. It is common to study these changes as time-varying FC (tvFC), by estimating FC within a temporally-ordered series of "windows." However, this approach is controversial, as fluctuations in tvFC can occur in the absence of cognitive processing, e.g. due to sampling variability. Therefore, linking tvFC to cognition, especially at rest, has proven challenging.

To address this challenge, we investigated the temporal dynamics of inter-subject similarity of tvFC during movie-watching and rest in a cohort of healthy adults (N = 29) undergoing fMRI scans. Specifically, we identified moments during movie-watching when subjects' tvFC patterns were more similar to each other than expected ($p < 0.01$; controlling for FDR). These high levels of similarity occurred due to the content of the movie and reflected intervals in time when subjects may have been engaged in similar cognitive processes. Interestingly, we found that these intervals were driven by increased inter-subject similarity of FC within many different brain systems, including attentional and default networks.

Next, we extracted representative FC patterns during intervals of high inter-subject similarity and characterized them using graph theoretic methods. We found that these patterns were less modular than those that occurred during periods of low inter-subject similarity ($p < 0.01$; controlling for FDR). This observation is in agreement with past studies reporting reduced modularity during cognitively demanding tasks, further suggesting that periods of high inter-subject similarity reflect shared cognitive processing.

Finally, we asked whether the FC patterns observed during intervals of high inter-subject similarity recurred during rest, i.e. in the absence of explicit task instructions. Indeed, we found

approximate recurrences of these FC patterns. This observation suggests that some fluctuations in tvFC during rest may reflect cognitive processes.

Disclosures: R. Betzel: None. **F. Zamani Esfahlani:** None. **L. Byrge:** None. **D.P. Kennedy:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.02

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DP1-HD091948

Title: Shared structure in neural activity across individuals during learning and during test facilitates performance in an introduction to computer science course

Authors: *M. MESHULAM, L. HASENFRATZ, H. HILLMAN, Y.-F. LIU, M. NGUYEN, K. A. NORMAN, U. HASSON;
Princeton Univ., Princeton, NJ

Abstract: How do students understand and remember new information? Despite major advances in measuring human brain activity during and after educational experiences, it is unclear how new knowledge is internalized and shared across minds. Here, we report results from a semester-long fMRI study examining neural activity during learning and during question answering. We hypothesized that shared structure in neural activity between learners and experts would emerge and reflect understanding of learned material.
24 undergraduate 'student' and five graduate 'expert' participants (11 female) were recruited for the study. The study was conducted in collaboration with Princeton's Department of Computer Science. Student participants were enrolled in Computer Science: An Interdisciplinary Approach (lectures available at informit.com). They were scanned every 2-3 weeks (six scans in total). During each of the first five scans, students watched 40 minutes of course lecture videos which were required viewing for the following week. On the final scan, students were shown five 3-minute 'recap' videos, each summarizing one lecture, then given a test requiring oral responses. Experts underwent the final scan only. All participants provided informed written consent in accordance with experimental procedures approved by the Princeton University IRB.
We found robust correlated activity across all students during lecture viewing. This activity spanned multiple brain regions, including superior temporal cortex and parietal areas, as well as visual and auditory cortex (inter-subject temporal and spatial correlation, $q<0.01$). Furthermore, student and expert neural activity patterns converged during recaps as well as during oral question answering. Crucially, similarity (to other students and to experts) was tightly linked to

performance, such that high-similarity individuals obtained better test scores. Thus, student-expert similarity in posterior cingulate cortex (PCC) during test was highly correlated with test score ($r=0.77$, $p>0.001$, permutation test). Lastly, within subjects, questions that evoked high neural similarity (to other students and to experts) were answered more accurately.
These results open a window into the mental processes underlying successful learning in a demanding, real-life college setting.

Disclosures: **M. Meshulam:** None. **L. Hasenfratz:** None. **H. Hillman:** None. **Y. Liu:** None. **M. Nguyen:** None. **K.A. Norman:** None. **U. Hasson:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.03

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1661016

Title: Brain-to-brain synchrony predicts long-term memory retention more accurately than individual brain measures

Authors: *I. DAVIDESCO, E. LAURENT, H. VALK, T. WEST, S. DIKKER, C. MILNE, D. POEPPEL;
New York Univ., New York, NY

Abstract: Our understanding of how the human brain learns while interacting with others in ecologically-valid environments is very limited. Recent studies have demonstrated that synchrony across brains ("brain-to-brain synchrony") can capture dynamic group interactions in classrooms (Bevilacqua et al., 2019; Dikker et al., 2017), but have not yet established the relationship between brain-to-brain synchrony and learning outcomes. Further, it is not clear if brain-to-brain synchrony can predict real-world outcomes better than individual brain measures. In the current study, EEG was concurrently recorded in a laboratory classroom from four students and a teacher during a science lesson. Our findings indicate that alpha-band (8-12Hz) brain-to-brain synchrony, but not alpha power or intra-brain alpha synchrony, significantly predicted memory retention a week after the lesson took place. Moreover, moment-to-moment variations in alpha-band brain-to-brain synchrony, but not alpha power, predicted what specific information was learned. Finally, while student-to-student brain synchrony best predicted delayed retention at zero lag, student-to-teacher brain synchrony best predicted delayed retention when the teacher's brain activity preceded that of the student by 200 msec. These findings provide critical evidence for the importance of brain data collected simultaneously from groups of individuals in ecologically-valid settings, and substantially extend the brain-as-predictor

approach by demonstrating that the predictive value of two brains can be greater than that of individual brains.

Disclosures: I. Davidesco: None. **E. Laurent:** None. **H. Valk:** None. **T. West:** None. **S. Dikker:** None. **C. Milne:** None. **D. Poeppel:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.04

Topic: H.02. Human Cognition and Behavior

Title: Shared and converging brain responses across people during self-guided exploration of complex photographs and paintings

Authors: *E. MUSZ, B. BELLANA, X. ZUO, J. CHEN;
Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: When an observer encounters a novel piece of art, her interpretation of the artwork may evolve over time, as she explores its components and builds an understanding of the relations between them. This dynamic and constructive process seems to unfold in an idiosyncratic way. While each person may take a different path, do they ultimately build the same final story? Which brain areas support this process? In this fMRI study, we tested whether shared perception and description of complex images elicits shared neural responses across people.

We measured brain activity and recorded verbal responses while participants viewed and described a series of five static images in a self-paced and self-guided manner. Each image depicted a complex scene with several people and objects. Participants were instructed to describe each picture in great detail (12 subjects, 6-23 minutes). During analysis, each image was segmented by experimenter-defined boundaries. Each participant's utterances and corresponding brain data were labeled according to 1) the segment described at each timepoint and 2) the level of detail provided ("general" or "specific").

We first tested whether each image segment elicited a distinctive multi-voxel activity pattern, and whether these patterns are shared across people. In the default mode network, we observed segment-specific activity patterns that were more correlated across people during descriptions of matching as opposed to non-matching segments, irrespective of the order in which segments were mentioned. This effect also emerged in visual cortex, but not early auditory cortex. These results are consistent with previous studies that have observed inter-subject pattern similarity using dynamic narrative stimuli (Chen et al. 2017). In addition, visual cortex was sensitive to level of detail, such that cross-subject pattern similarity was greater during "specific" statements,

relative to “general” statements. Future analyses will test whether individuals' brain activity converges over time, modulated by the similarity of their image exploration trajectory.

Disclosures: **E. Musz:** None. **B. Bellana:** None. **X. Zuo:** None. **J. Chen:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.05

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 MH112566-01
NIH Grant 5DP1 HD091948-02

Title: Brain-to-brain coupling during teaching and learning

Authors: ***M. NGUYEN**[1], A. CHANG[1], M. MESHULAM[1,2], S. NASTASE[1,2], U. HASSON[1,2]; [1]Dept. of Psychology, [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Human communication is remarkably versatile, enabling teachers to share highly abstracted and novel information with their students. What neural processes enable such transfer of information across brains during real-life, complex communication in the classroom? Here, we address this question using functional MRI in a lecture setting, wherein information

transmission is unidirectional and flows from the teacher's brain to the student's brain. We hypothesized that the effect of teaching is to bring the student's brain into alignment with the teacher's as a function of learning. In the Teaching phase, we scanned an expert teacher (N=1, female) in fMRI giving a 32-minute oral lecture with slides on a technical, scientific topic, followed by a 6-min review. The teacher gave the same lecture and review 5 times in the scanner. In the Learning phase, we scanned students (N=22, 15 female) watching the lesson and review on two consecutive days: on Day 1, students completed a pre-learning quiz and watched the main lecture, and on Day 2, students watched the review and completed a post-learning quiz. Using intersubject spatial pattern similarity, we first identified regions in the Teacher brain that were reliably correlated across the teaching sessions. These regions extended from early sensory cortices to linguistic regions along the superior temporal sulcus to higher-level regions including posterior medial cortex (PMC), superior parietal lobule (SPL), and widespread regions of dorsolateral and dorsomedial prefrontal cortex. During learning, we observed correlation across students in similar regions, as well as significant reinstatement of response patterns from the lesson during the review. Finally, we observe widespread teacher-student correlation during both the lesson and the review, with the students' neural responses yoked to the teacher's at a short lag. Furthermore, teacher-student correlation in high-level regions, including PMC, bilateral temporal parietal junction (TPJ), and right SPL, was significantly correlated with learning outcomes: the more closely the student's brain mirrored the teacher's brain, the better the student's post-lesson behavioral score. Together, these results suggest that the alignment of neural responses between teacher and students may underlie effective communication of complex information across brains in classroom settings.

Disclosures: M. Nguyen: None. **A. Chang:** None. **M. Meshulam:** None. **S. Nastase:** None. **U. Hasson:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.06

Topic: H.02. Human Cognition and Behavior

Title: An interbrain approach for understanding empathy

Authors: *S. G. S. SHAMAY-TSOORY[1], P. GOLDSTEIN[2];
[1]Psychology, [2]Univ. of Haifa, Haifa, Israel

Abstract: Empathy allows us to understand and share one another's emotional experiences. Despite the developments in the study of empathy, the vast majority of empathy paradigms focus only on passive observers, carrying out artificial empathy tasks in socially deprived environments. This approach significantly limits our understanding of interactive aspects of

empathy and how empathic responses affect the distress of the sufferer. We recently proposed a brain model that characterizes how empathic reactions alleviate the distress of a target. Specifically, in a dual-EEG study we show that hand-holding during pain administration increases brain-to-brain coupling in the alpha-mu band in a network that mainly involves the central regions of the pain target and the right hemisphere of the empathizer. Moreover, brain-to-brain coupling in this network was found to correlate with analgesia magnitude, indicating that brain-to-brain coupling may contribute to touch-related analgesia. Similarly, using a serial dual-fMRI approach we show a shared activity between the target and the empathizer during hand-holding. Employing this dual-brain approach may provide a highly controlled setting in which to study the neuroanatomical bases of real-life empathy and its contribution to distress regulation.

Disclosures: S.G.S. Shamay-Tsoory: None. **P. Goldstein:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.07

Topic: H.02. Human Cognition and Behavior

Title: Lipreading and listening naturalistic narratives

Authors: *M. E. SAMS[1], M. BACHA-TRAMS[2], E. GLEREAN[2], U. HASSON[3], I. P. JÄÄSKELÄINEN[2], S. SAALASTI[2], J. M. LAHNAKOSKI[2];
[2]Neurosci. and Biomed. Engin., [1]Aalto Univ., Espoo, Finland; [3]Dept. of Psychology, Princeton Univ., Princeton, NJ

Abstract: We estimated the similarity of brain activity during lipreading, listening, and reading of the same 8-min narrative of 29 subjects whose lipreading skill varied extensively. The narrative was either comprehensible or gibberish Finnish, the latter being phonetically correct but incomprehensible. It was created by replacing consonants from each word of the original narrative with other consonants with similar place of articulation, but the suffixes that indicated syntax were kept unchanged. The similarity of subjects' brain activity within and between conditions was estimated by voxel-wise comparison of the BOLD signal time courses. Inter-subject correlation (ISC) of the time courses revealed that lipreading and listening the narrative were supported by the same brain areas in temporal, parietal and frontal cortices, precuneus and cerebellum. However, lipreading activated only a small part of the neural network that is active during listening/reading the narrative. Skilled lipreading was associated specifically with bilateral activity in the superior and middle temporal cortex, which also encode auditory speech. Interestingly, during lipreading gibberish narrative, ISC in visual cortical areas was much more extensive and extended to the superior temporal gyrus and sulcus, motor cortex, and cerebellum. When subjects listened to the narrative, significant bilateral ISC for the intact narrative was

found in extensive cortical areas: Bilaterally in the auditory and peri-auditory cortices, in the superior temporal gyrus and sulcus, in the middle temporal gyrus and sulcus, in the inferior parietal lobule, in visual cortex and in cerebellum. In the left hemisphere significant ISC was found in superior frontal gyrus, precentral gyrus and inferior frontal gyrus. In midline, significant ISC was found bilaterally in precuneus, and medial prefrontal cortex. Instead, during listening to gibberish narrative, significant ISC was restricted to the bilateral middle STG/S and MTG, the motor cortex, and midline visual cortex. Significant ISC in more extensive cortical areas during lipreading gibberish rather than intact narrative might be related to gibberish being equally incomprehensible to all subjects (in contrast to lipreading), and therefore being processed more similarly and likely with more effort than intact narrative. Listening to gibberish narrative activated auditory and phonetical processing areas, as well as parts of cerebellum and midline visual cortex quite similarly in different speakers, probably reflecting processing narrative's phonological features.

Disclosures: M.E. Sams: None. **M. Bacha-Trams:** None. **E. Glerean:** None. **U. Hasson:** None. **I.P. Jääskeläinen:** None. **S. Saalasti:** None. **J.M. Lahnakoski:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.08

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 603503991

Title: Students watching educational videos with high inter-subject correlation obtain high test scores

Authors: *J. MADSEN[1], S. S. COHEN[1], S. JULIO[1], P. GUCIK[1], R. STEINBERG[2], L. C. PARRA[1];
[1]Biomed. Engin., [2]Dept. of Physics, City Col. of New York, New York, NY

Abstract: Online educational materials are largely disseminated through videos, and yet little is known about how effective the video material is at captivating the audience and in the end communicating the material. Even less is known about how to measure how attentive students are while watching educational videos and in the end how much they learn from the video. We hypothesize that attentive students follow educational videos similarly with their eyes and brain. We find that inter-subject correlation of eye movements and electroencephalography correlated to one another, and substantially higher when students watch videos attentively compared to when they are distracted. Given the link between attention and memory we predicted that similarity of eye-movement and electroencephalography with a group of students is predictive of

subsequent performance in a test on the educational material. We show that inter-subject correlation of eye movements and electroencephalography is predictive of individual test scores for recall and comprehension questions alike. These findings replicate using videos produced for online education in a variety of styles and learning contexts. These results suggest that EEG and eye movements can be used as marker of attentional mechanisms necessary to retain information. In the future, EEG and eye movements may be used as a tool to design and assess online educational content as well as track student attention in real time.

Disclosures: J. Madsen: None. **S.S. Cohen:** None. **S. Julio:** None. **P. Gucik:** None. **R. Steinberg:** None. **L.C. Parra:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.09

Topic: H.02. Human Cognition and Behavior

Support: NWO VENI Grant 275-89-018

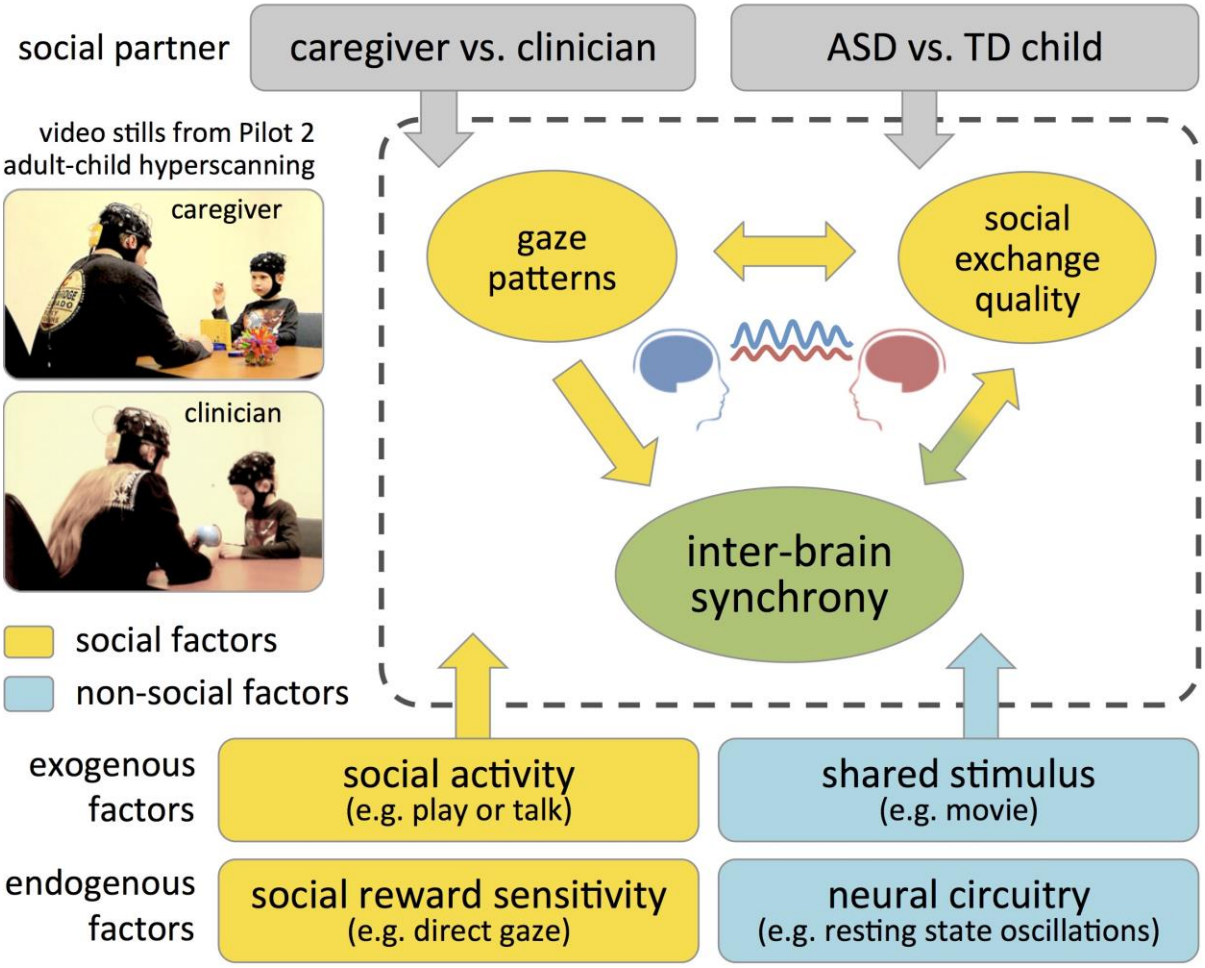
Title: The clinical relevance of studying the neurobiology of real-world dynamic social interactions

Authors: S. DIKKER[1], *D. BEVILACQUA[1], G. DUMAS[2], E. AJODAN[3], E. CLARK-WHITNEY[3], R. JONES[3];
[1]New York Univ., New York, NY; [2]Inst. Pasteur, Paris, France; [3]Sackler Inst. for Developmental Psychology, New York, NY

Abstract: Recent methodological advances have enabled researchers to investigate how the human brain supports real-world dynamic social interactions. We present two series of experiments that illustrate possible clinical implications of this “interactive turn”. For Part 1, while Autism Spectrum Disorder (ASD) is characterized by impairments in social communication, its neurobiology is typically not investigated during dynamic face-to-face exchanges. In addition, how the ongoing social dynamics —including gaze behavior— modulate the neural dynamics has not been systematically investigated in ASD. In two studies, we recorded gaze behavior and electroencephalography (EEG hyperscanning) during naturalistic interactions between children with ASD and a caregiver and a clinician. In Study 2, inter-brain synchrony (inter-subject Phase Locking Value (PLV) of neural activity in the alpha (8-12 Hz) and beta (12-20 Hz) frequency bands, averaged across the interaction) varied as a function of the social partner, context, and direct gaze. Direct gaze was associated with an increase in inter-brain synchrony. Further, child-adult inter-brain synchrony was higher if there was no toy present during the interaction, and this difference was most pronounced when children interacted with a

caregiver as opposed to a clinician. For Part 2, direct gaze, the social partner, and social aptitude also predicted inter-brain synchrony in a series of studies on healthy adults: during dyadic and group face-to-face interactions, empathic personality traits, joint action, and social connectedness were all found to be associated with an increase in inter-brain synchrony, highlighting their role during real-world perception and communication. Taken together, simultaneous EEG and gaze-tracking can provide critical insight into the brain basis of real-time social interactions and increase our understanding of core mechanisms driving social communication and social deficits.

Fig1. Factors driving adult-child inter-brain synchrony



Disclosures: **S. Dikker:** None. **D. Bevilacqua:** None. **G. Dumas:** None. **E. Ajodan:** None. **E. Clark-Whitney:** None. **R. Jones:** None.

Nanosymposium

274. Social Cognition: Behavior and Neural Mechanisms II

Location: Room S401

Time: Monday, October 21, 2019, 8:00 AM - 10:30 AM

Presentation Number: 274.10

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 MH112566-01

Title: Tracking neural alignment due to natural conversation

Authors: B. SIEVERS[1], C. WELKER[2], *T. WHEATLEY[2];
[1]Psychology, Harvard Univ., Cambridge, MA; [2]Psychological and Brain Sci., Dartmouth, Hanover, NH

Abstract: Short conversations can create lasting changes in belief. Scaled up to the level of the community or society, these changes have profound effects. We present a neuroimaging and social network study of how conversation changes belief, testing three hypotheses: (1) coming to a consensus due to conversation manifests as increased synchronization of neural activity, (2) social influence is, at its core, neural influence—influential people shape others' brain patterns to become more like their own, and (3) people who exert strong neural influence hold privileged (central) positions in their social networks. Participants (students at Dartmouth's Tuck School of Business) completed an online social network survey. They then viewed 5 silent movie clips with ambiguous narrative content during functional magnetic resonance imaging (fMRI). Afterward, participants split into small groups and engaged in unstructured discussion of the movie clips with the goal of coming to a consensus interpretation of their content. Participants then underwent a second fMRI scan, viewing the same movie clips again as well as a set of novel clips from later in each movie. We show increased neural intersubject correlation and pattern similarity across a network of brain areas within discussion groups compared to other groups and control groups for both the original and novel movie clips. We also show that this increased synchrony is not achieved by equal adaptation within the group but that some group members exert more "pull" on the alignment than others. The neural influence was predicted by members' centrality in the real-world social network they share. This approach demonstrates a novel measure of neural influence and elucidates the relationship between neural influence and social network centrality.

Disclosures: B. Sievers: None. **C. Welker:** None. **T. Wheatley:** None.

Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

Location: Room S404

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 275.01

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant U01MH105982

Title: Cross areal cellular diversity in human cortex

Authors: *T. E. BAKKEN, R. D. HODGE, J. A. MILLER, Z. YAO, S.-L. DING, L. T. GRAYBUCK, J. GOLDY, J. CLOSE, D. BERTAGNOLLI, S. I. SHEHATA, C. RIMORIN, A. TORKELSON, M. TIEU, T. CASPER, D. MCMILLEN, T. PHAM, A. GLANDON, K. WARD, J. SULC, K. CRICHTON, H. TUNG, E. BARKAN, M. KROLL, N. DEE, S. M. SUNKIN, K. SMITH, C. KOCH, B. TASIC, H. ZENG, E. LEIN;
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Abstract: The human cortex is composed of billions of neurons that are wired into local circuits with long-range connections and distributed across at least 100 functionally and anatomically distinct areas. Decades of research have revealed conserved and strikingly divergent cellular properties across the cortical sheet. It is an open question to what degree there is a core set of cell types that are shared across areas but with specialized features or novel cell types specific to areas. This study used single nucleus RNA-sequencing of post-mortem adult human brain to deeply sample (n > 50,000) transcriptional diversity of cells in four primary sensorimotor areas (M1, S1, A1, and V1) and two association areas (anterior cingulate, middle temporal gyrus). Iterative clustering identified over 150 transcriptomic clusters with distinct distributions across cortical layers and marker genes. Consistent with a recent report for mouse, GABAergic interneurons and non-neuronal cells are highly similar across cortex while glutamatergic neurons demonstrate clear areal signatures. Distant projection targets could be predicted for excitatory types based on alignment with mouse cell types based on shared co-expression signatures. Based on this analysis, rare populations of layer 5 neurons that putatively project to extratelencephalic structures vary 10-fold in frequency across human cortical areas. Compared to rodents, primates have higher visual acuity and a much larger primary visual cortex with distinct cytoarchitecture. We find expanded cellular diversity in V1 compared to other human cortical areas, including two V1-specific interneuron types and more distinct excitatory types in granular and subgranular layers. These data enable comparisons of cortical circuit components between human and other mammals in functionally matched areas that may lead to a better understanding of the evolution of cell types.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

Location: Room S404

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 275.02

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant U01MH114825
NIH Grant F32NS103266

Title: Understanding progenitor and neuronal cell type identity in the developing human brain

Authors: *A. BHADURI, U. EZE, M. ANDREWS, C. SANDOVAL-ESPINOSA, T. NOWAKOWSKI, A. KRIEGSTEIN;
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Abstract: The human brain is composed of diverse cell types across brain regions that enable unique capabilities. Within the brain, the cerebral cortex is responsible for a number of cognitive functions and sensory integration, with distinct cortical regions controlling a variety of tasks including motion, vision, speech, and judgment. In order to understand how neurons of the distinct cortical regions are specified, we performed single-cell RNA sequencing across twenty developing human brains during first and second trimester stages of development, generating over 1.5 million cells. From these data, we identify a small number of subpopulations of neuroepithelial cells and highlight several key pathways that may regulate the switch from neuroepithelia to radial glia identity. During peak neurogenesis, we identify hundreds of cells types including temporal and area specific neurons, interneurons and radial glia populations, as well as a number of subtypes from each of these classes that are expressed across most cortical areas. By comparing these cell types to those that are generated in cerebral organoids, we observe that *in vitro* models of cortical development strongly recapitulate broader hierarchies of cell identity, such as cell class, type and state, but clearly do not possess identifiers of cell subtypes that exist in normal human development. Together, these data suggest a model of area and subtype specified progenitors that give rise to area specific neuronal types. Moreover, the contrast to organoid cell types indicates that broad cell type can be sufficiently directed *in vitro,* but that subtype specification at the earliest stages of development is regulated by fine-tune signals that are not present in the organoid. These subtypes may be required for precise cell type identity in post-mitotic, differentiated cells.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

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Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 275.03

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant U01MH114819

Title: Innovations in interneuron repertoire across mice and primates

Authors: *F. M. KRIENEN[1,4], M. GOLDMAN[2], Q. ZHANG[5], R. DEL ROSARIO[4], M. FLORIO[2], R. MACHOLD[7], A. SAUNDERS[2], K. LEVANDOWSKI[5], H. ZANIEWSKI[5], B. SCHUMAN[8], C. WU[5], A. LUTSERVITZ[2], C. MULLALLY[2], N. REED[2], E. BIEN[2], L. BORTOLIN[2], M. FERNANDEZ-OTERO[4], J. LIN[4], A. WYSOKER[4], J. NEMESH[4], D. KULP[4], M. BURNS[5], V. TKACHEV[9], R. SMITH[9], C. A. WALSH[9], J. DIMIDSCHSTEIN[4], B. RUDY[7], L. KEAN[9], S. BERRETTA[10], G. J. FISHELL[3,4], G. FENG[6,4], S. MCCARROLL[1,4];
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Abstract: The effective study of brain disorders, cognition, genetic perturbation, and therapeutics will require experimental models that are well-understood and relevant to human biology. I will describe our work to compare cellular composition and gene utilization across the brains of adult mice, marmosets, macaques, and humans, using single-cell RNA sequencing (Drop-seq) to profile hundreds of thousands of brain cells or nuclei. Interneurons within the cerebral cortex and related structures release the inhibitory neurotransmitter GABA, participate in local assemblies and provide the main source of inhibition in neuronal circuits. They make an interesting test case for comparative analysis because they are morphologically and physiologically diverse, yet molecular types are broadly conserved. Focusing on interneurons, we present evidence of four ways evolution alters the composition of a brain structure: changing proportions of conserved cell types, changing the molecular composition of conserved cell types, reallocating cell types across structures, or inventing new types. Taken together, these results reveal new insights into how relatively closely related brains diversify their cellular and molecular repertoire. Understanding the ways in which interneurons might have evolved in primates versus mice can guide the appropriate choice of models for studying how local microcircuits and excitatory/inhibitory balance are affected in human disease.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

Location: Room S404

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 275.04

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Single cell chromatin accessibility profiling reveals distinct epigenome landscape in developing and adult mouse brain

Authors: *L. WANG, F. MESCHI, C. NEMEC, J. WANG, A. PULEO, P. SHAH, B. OLSEN, A. GONZALEZ, P. GIRESI, G. ZHENG;
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Abstract: Dissecting the cis-regulatory network is one of the central tasks to understand the non-coding genome and the physiology of complex tissues. Epigenetic profiling at the single cell level is an emerging technique that has created unprecedented opportunities to tackle this challenge. However, existing protocols suffer from low sensitivity across the large range of tissue types and tools designed for single cell RNA-seq (scRNA) data are not suitable for analyzing the highly sparse, high dimensional single cell epigenome profiling data. We have developed a single cell ATAC (scATAC) solution that provides a robust and scalable approach for profiling chromatin accessibility in tens of thousands of individual nuclei. This solution is applicable to various sample types including fresh, cryopreserved and flash frozen tissues. We have provided a computational pipeline that enables efficient processing of scATAC data and characterization of the dynamics of cis-regulatory elements and transcription factor activities.
To extend our dissection of the epigenetic regulatory networks, we profiled chromatin accessibility of ~10,000 cells from developing and adult mouse cerebral cortex and designed an automatic cell type annotation strategy for scATAC data. Similar to gene expression, chromatin accessibilities of excitatory neurons display regional specificity in each layer of the cortex, while inhibitory neurons form subtype clusters defined by marker gene expression. We also observed enhanced neuron type diversification and increased differentiation of glial cells in adult cortex, compared to the embryonic counterpart at E18.5. Finally, by combining data from embryonic and adult brain cortex, we constructed transcription factor interaction networks and identified cis-regulatory elements with dynamic accessibility during neurogenesis.
Taken together, our studies lead to novel mechanistic insights into regulatory networks between the epigenome and the transcriptome and provides an easy-access computational pipeline for complex analysis of scATAC data.

Disclosures: L. Wang: A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **F. Meschi:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics.

C. Nemec: A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **J. Wang:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **A. Puleo:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **P. Shah:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **B. Olsen:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **A. Gonzalez:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **P. Giresi:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **G. Zheng:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics.

Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

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Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

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Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant 1U19MH114831-01

Title: Linking projection neuron types to epigenetic profiles by single-cell methylome sequencing

Authors: *Z. ZHANG[1], J. ZHOU[1,6], Y. PANG[2], A. RIVKIN[1], P. A. MIYAZAKI[2], A. BARTLETT[1], A. ALDRIDGE[1], J. R. NERY[1], R. CASTANON[1], M. RASHID[2], M. VU[2], M. JACOBS[2], T. ITO[2], E. WILLIAMS[3], J. B. SMITH[3], C.-T. LEE[4], K.-F. LEE[4], X. JIN[3], M. BEHRENS[5], E. A. MUKAMEL[7], E. M. CALLAWAY[2], J. R. ECKER[1,8];
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Abstract: Molecular properties and anatomy are both central defining features for neuronal cell types and functions. While recent advances in single cell genomics have led to high-resolution molecular characterizations of cell type diversity in the brain, neuronal cell types are often studied out of the context of their anatomical properties. Our study aims to link molecular properties of cell types to neuronal connectivity by combining retrograde tracing with single cell DNA methylome sequencing. As part of the effort of our Center for Epigenomics of the Mouse Brain Atlas (CEMBA), we systematically label neurons with defined long-distance projection targets throughout the adult mouse brain using a viral strategy (AAVretro). We isolate nuclei from labeled neurons and characterize their epigenetic signatures by single-nucleus methylome sequencing (snmC-seq2). We have profiled 72 distinct long-distance projections, with a focus on projections originating from cortical regions including primary motor cortex (MOp), primary somatosensory cortex (SSp), anterior cingulate cortex (ACA), agranular insular cortex (AI), primary auditory cortex (AUDp), retrosplenial cortex (RSP), posterior parietal cortex (PTLp), and primary visual cortex (VISp). From each of these regions we isolate neurons projecting to various subcortical targets including striatum (STR), superior colliculus (SC), thalamus (TH), pons (P), and medulla (MY). To ensure high-resolution and high-quality DNA methylation profiling of the projecting neurons, we generate single nuclei DNA methylome profiles for at least 250 neurons of each projection. With these data, we are, for the first time, able to examine the epigenetic identity of these distinct groups of projection neurons. In addition to revealing distinct excitatory neuron clusters that correspond to their laminar and spatial locations, we have also identified unique DNA methylation patterns in both CG and non-CG sequence contexts that are signatures of specific cortico-subcortical projections. Our results show that the laminar location, cortical region, and projection target all contribute to the unique epigenetic signatures of individual neurons. To validate these findings we are identifying genes that are uniquely expressed in neurons of specific projections. Our data can also identify potential regulatory sequences such as enhancers that could be tested to specifically target and label each projection neuron type, enabling the targeted study and manipulation of projection neurons of interest.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

Location: Room S404

Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 275.06

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant MH114831

Title: Single cell analysis of gene regulatory elements in the mouse brain

Authors: *Y. E. LI[1], S. PREISSL[3], R. FANG[4], X. HOU[3], O. POIRION[3], X. WANG[3], J. Y. HAN[3], J. LUCERO[5], S. KUAN[2], J. CHIOU[6], D. GORKIN[3], E. MUKAMEL[7], K. GAULTON[6], M. BEHRENS[8], J. R. ECKER[9], B. REN[2];
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Abstract: The mammalian brain consists of hundreds of cell types that work together to carry out the diverse neurological functions.To understand how neuro circuits form and how their functions are supported by various non-neuronal cell types, it is important to identify and characterize the *cis*-regulatory sequences in each cell type. Here, we employed a combinatorial barcoding-assisted single-cell assay for transposase-accessible chromatin (sci-ATAC-seq) to profile chromatin accessibility in more than 1,000,000 cells from 26 cortical and subcortical regions of the rostral mouse brain. The resulting chromatin accessibility maps reveal 125 cellular taxonomy in the neocortex, olfactory bulb, hippocampus, basal ganglia and striatum, and delineate highly cell-type specific usage of ~350k potential regulatory DNA elements. Further integrative analysis uncovers transcription factor networks involved in each cell type, and potential cell types involved in human neurological disease. This rich resource of chromatin accessibility in the mouse brain at single cell resolution lays the foundation for understanding the gene regulatory program in the mammalian brain.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

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Time: Monday, October 21, 2019, 8:00 AM - 10:15 AM

Presentation Number: 275.07

Topic: I.02. Systems Biology and Bioinformatics

Support: R24MH114788
R24MH114815

Title: NeMO analytics: A multi-omic visualization and analysis resource for the BRAIN initiative

Authors: *S. A. AMENT[1,2], J. ORVIS[3], B. GOTTFRIED[3], A. CHATTERJEE[3], J. KANCHERLA[8], B. HERB[3], A. M. CASELLA[3,4], K. ROSE[5], H. CORRADA BRAVO[8], C. COLANTUONI[3], A. MAHURKAR[3], O. WHITE[3], R. HERTZANO[3,6,7];
[2]Psychiatry, [3]Inst. for Genome Sci., [4]Physician Scientist Training Program and Program in Mol. Med., [5]Program in Mol. Med., [6]Dept. of Otorhinolaryngology-Head & Neck Surgery, [7]Anat. and Neurobio., [1]Univ. of Maryland Sch. of Med., Baltimore, MD; [8]Competer Sci., Univ. of Maryland at Col. Park, College Park, MD

Abstract: The multi-omic data generated by the BRAIN initiative is now archived in the Neuroscience Multi-Omic Archive (NeMO Archive). The data are archived as flat files with the primary purpose to enable downloads by bioinformaticians and are not readily accessible to researchers not trained in programming. To address this, we have initiated NeMO Analytics (nemoanalytics.org), a portal designed to allow a broad range of neuroscientists to fully benefit from the wealth, breadth and depth of the multi-omic data generated by the BRAIN initiative without requiring any expertise in programming. NeMO Analytics gene expression tools are powered by gEAR (umgear.org) and consist of seven components: (i) An expression browser, which allows the visualization of gene expression across datasets; (ii) A comparator tool for basic comparison of all of the genes in two groups; (iii) a clustering and projection tool to identify groups of genes with similar expression patterns and the dynamics of these genes across datasets; (iv) An elaborate single cell workbench; (v) A dataset uploader, which allows seamless integration with the NeMO Archive data portal for data import, as well as import of user-supplied datasets in a market exchange format (MEX); (vi) A dataset curator that allows the user to define visualization preferences (e.g., data presentation as bar, line, x-y scatter, violin plot, tSNE, or SVG); and (vii) A dataset manager, which allows the selection of groups of datasets to visualize side-by-side and manage dataset sharing. NeMO Analytics also allows the visualization of epigenomic data in the context of a linear genome browser via integration with Epiviz (https://epiviz.github.io/).We have seeded this instance of NeMO Analytics with high-value datasets related to neocortical development, as well as with multi-omic single-cell data from the primary motor cortex, generated by the BRAIN Initiative Cell Census Network (BICCN). The portal is expanding rapidly to include data from additional regions of the developing and adult brain. Users can interrogate these datasets using the tools described above.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

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Presentation Number: 275.08

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: U19MH114821-02
Crick-Clay Professorship at Cold Spring Harbor Laboratory
H N Mahabala Chair Professorship at IIT Madras

Title: A computational methodology for reconciling brain atlas hierarchies within and across species

Authors: *B.-X. HUO, P. P. MITRA;
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Abstract: Reference atlases for brains are widely used in the neuroscience community. However, for any given species, multiple reference brains and atlases exist due to subjective region boundaries delineated by individual neuroanatomists, as well as technical variations in tissue processing and imaging methods. These reference spaces led to different potential parcellations, manifested in various hierarchical organizations within the same species. Further, comparative analysis of brain hierarchies across species adds another layer of complexity where the phylogenetic diversity of different brain architectures need to be considered while respecting homological relationships. A rigorous strategy is therefore desirable to reconcile atlas hierarchies within species and properly interpreting cross-species homologies. We present a computational methodology to address these issues for objectively comparing atlas hierarchies in order to achieve potential reconciliation. The methodology is as follows. Starting with leaf-level structures in the hierarchy, the compartments with similar annotations are matched, reflecting concordance of the region within the species, or homology across species. Certain leaves in one tree could be further divided in another tree hence corresponding to the branching nodes. Such leaf-to-node correspondence reflects heterogeneous views on region parcellation within the species, or proliferation or reduction across species. Finally, unique leaves to individual trees are identified as key structures in reconciling the hierarchies. Once there is leaf-level agreement, the trees built from these leaves can be computationally compared, and reconciled using a tree-edit distance. We applied this framework for within-species hierarchical comparison using reference mouse brain atlases (Paxinos & Watson 1998; AIBS 2008); as well as for cross-species comparison between mouse and marmoset brains (Hashikawa et al. 2015). For cross-species comparison, over 80% of the gray matter volumes in either species were matched, despite the large discrepancy between hierarchical structures. Our results highlighted the consensus on leaf-level brain regions and provided computational methodology to compare the common, as well as unique, brain regions in each atlas.

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Nanosymposium

275. Single-Cell Analysis of Cortical Cell Type Diversity

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Presentation Number: 275.09

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NIH R01 MH109901
NIH R01 MH110928
NIH U01 MH103339

Title: BrainVar data set: Whole-genome and RNA sequencing reveal variation and transcriptomic coordination in the developing human prefrontal cortex

Authors: *D. M. WERLING[1], S. POCHAREDDY[2], J. CHOI[2], J.-Y. AN[3], B. SHEPPARD[4], M. PENG[5], Z. LI[2], G. SANTPERE[2], F. O. GULDEN[6], M. S. BREEN[7], M. E. TALKOWSKI[8], K. ROEDER[5], M. STATE[4], B. DEVLIN[9], S. SANDERS[4], N. SESTAN[2];
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Abstract: Variation in gene expression across age, cell type, and brain region underlies typical brain development and function, while genetic variants contribute to risk for neuropsychiatric disorders. To examine gene expression and neuropsychiatric risk across human cortical development, we generated BrainVar, a unique resource of whole-genome and RNA sequencing from the post mortem human dorsolateral prefrontal cortex of 176 neurotypical donors (104 male, 72 female) aged 6 post-conception weeks to 20 years. Sequencing data were aligned to the GRCh38 reference, gene-level read counts calculated by HTSeq, and DNA variants called using GATK Haplotype Caller. From 23,782 cortically expressed genes, we used Flexmix to classify genes into rising, falling, and non-transitional temporal trajectories, Weighted Gene Co-expression Network Analysis to identify 19 co-expression modules, and linear regression in Hail to find 252,629 common (≥5% frequency) cis-expression quantitative trait loci (eQTLs) associated with 8,421 genes (eGenes). We find that gene sets with prenatal peak expression, whether defined by co-expression module or a falling temporal trajectory, are more likely to be haploinsufficient, enriched for developmental disorder risk genes, and enriched for neuronal precursor genes; rising genes enrich for glial and adult excitatory neuron genes. We also observe

a late fetal phase of widespread expression changes that likely reflects shifting cell type proportions and cellular processes. eQTLs with constant effects across development are enriched for common variant neuropsychiatric disorder risk loci, while eGenes exhibiting prenatal- or postnatal-differential effects more closely resemble disorder risk genes in that they are more likely to be protein-coding, haploinsufficient, and more strongly connected within co-expression and protein interaction networks. These patterns suggest that evolutionary constraints limit the population frequency or the magnitude or timing of impact of eQTLs on key developmental processes. Collectively, these results underscore the utility of evaluating developmental trajectories for understanding typical and pathological physiology, and the BrainVar resource will facilitate future studies on human development, neurobiology, and neuropsychiatric disorders.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

Location: Room S405

Time: Monday, October 21, 2019, 1:00 PM - 3:30 PM

Presentation Number: 352.01

Topic: A.07. Developmental Disorders

Support: NIH R01 Grant MH116500

Title: Synaptic and circuit mechanisms of visual experience-dependent impairments in Fmr1 KO mice

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Abstract: Fragile X syndrome (FXS) is the most common inherited form of autism and intellectual disability. Previous work has demonstrated impaired mGluR-dependent long-term depression (LTD) and long-term potentiation (LTP) in Fmr1 KO mice, the mouse model of FXS. Recent studies have shown hyperactivity of the overall neuronal circuit and hypoactivity of parvalbumin-positive fast-spiking interneurons in the primary visual cortex (V1) of Fmr1 KO mice. However, how experience affects synaptic and circuit plasticity in Fmr1 KO mice, and how impairments in these forms of plasticity may lead to the alterations in the visual perception and learning is poorly understood. We have recently discovered a new form of visual familiarity-dependent oscillations. These oscillations can be blocked by the muscarinic receptor antagonists and may influence visual information processing in V1. To study how visual familiarity (a form

of learning in V1) is impaired in Fmr1 KO mice, we have used a comprehensive approach including channelrhodopsin-2 assisted circuit mapping (CRACM) in visual cortex slices, in vivo extracellular recording using high-density silicon probes, pupillometry, and behavior. We have discovered attenuation in the duration and magnitude of the familiarity-induced oscillations and their frequency shift in Fmr1 KO mice. This attenuation was correlated with the decreased stimulus-specific adaptation of the transient pupil dilation, a biomarker of surprise response. We have identified an oscillatory neural circuit in V1 formed after the visual experience, which consisted of the intrinsically bursting (IB) layer 5 pyramidal cells, fast-spiking (FS) interneurons in layer 4 and layer 2/3 regular-spiking (RS) cells. Using a combination of in vivo directed information analysis and in vitro circuit mapping, we have discovered that the layer 5-layer 4 FS connection is weaker in Fmr1 KO mice which may serve as the underlying mechanism for the weaker oscillations in vivo.

Disclosures: S.T. Kissinger: None. **Q. Wu:** None. **C.J. Quinn:** None. **A.A. Chubykin:** None.

Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

Location: Room S405

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Presentation Number: 352.02

Topic: A.07. Developmental Disorders

Support: NICHD
SFARI
DOD

Title: Dissecting circuit dynamics underlying impaired perceptual learning in a mouse model of autism

Authors: *A. GOEL[1], L. SCHMITT[2], G. CHAUDHARI[3], B. TODISCO[1], N. AHMED[3], E. PEDAPATI[2], C. A. ERICKSON[2], C. PORTERA-CAILLIAU[3];
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Abstract: Atypical sensory processing, including a profound propensity for sensory distraction, is often observed in Fragile X Syndrome (FXS) and can be predictive of future deficits in social behavior and in learning and memory. To examine abnormal cortical dynamics that contribute to deficits in learning, we used a go/no-go visual discrimination task for head-restrained mice in which animals learned to associate a water reward with a ‘preferred’ orientation of drifting sinusoidal gratings. We discovered that *Fmr1*$^{-/-}$ mice, the most commonly used animal model of FXS, take significantly longer to learn to discriminate between gratings drifting in two orthogonal orientations compared to wild-type (WT) mice. Using an analogous task for human

subjects, we also found similar deficits in visual processing in FXS participants. Interestingly, introducing an auditory distractor during the task further impaired the discriminatory performance in both *Fmr1*$^{-/-}$ mice and humans with FXS but did not affect WT mice or control human subjects. To examine the circuit mechanisms that contribute to this detrimental impact of sensory hyperarousal on learning, we used in vivo two-photon calcium imaging (GCaMP6s) to record network dynamics in layer 2/3 of primary visual cortex (V1). We found a significantly lower fraction of and broader tuned orientation selective pyramidal cells in V1 in *Fmr1*$^{-/-}$ mice compared to WT mice, which correlated with the poor performance of *Fmr1*$^{-/-}$ mice on the visual discrimination task.
Because a defect in inhibition is a central problem in FXS, we selectively recorded calcium signals from parvalbumin (PV) inhibitory interneurons and found a decrease in functional output of PV neurons in *Fmr1*$^{-/-}$ mice. PV interneurons in sensory areas are known to sharpen orientation tuning of pyramidal cells and indirectly modulate attention via alterations in cortical gain, both of which can affect visual feature detection and ultimately sensory discrimination. Strikingly, we found that restoring normal PV cell activity with designer receptors exclusively activated by designer drugs (DREADDs) was sufficient to rescue the perceptual learning deficit in *Fmr1*$^{-/-}$ mice and also improved orientation tuning in pyramidal neurons. Vasoactive Intestinal Polypeptide (VIP) cells is a group of interneurons that dynamically regulate sensory responses and plasticity as a function of the behavioral brain state of the animal. To examine the contribution of abnormal brain states and hyperarousal to the behavioral deficits in *Fmr1*$^{-/-}$ mice, we are currently examining the contribution of PV and VIP neurons during perceptual learning in *Fmr1*$^{-/-}$ and WT mice in the presence of sensory distractors.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

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Title: Reduced prefrontal synaptic connectivity and disturbed oscillatory population dynamics in the CNTNAP2 model of autism

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Abstract: Loss-of-function mutations in CNTNAP2 cause a syndromic form of autism spectrum disorder in humans and produce social deficits, repetitive behaviors, and seizures in mice. Yet, the functional effects of these mutations at cellular and circuit levels remain elusive. Using laser-scanning photostimulation, whole-cell recordings, and electron microscopy, we found a dramatic decrease in excitatory and inhibitory synaptic inputs onto L2/3 pyramidal neurons of the medial prefrontal cortex (mPFC) of Cntnap2 knock-out (KO) mice, concurrent with reduced spines and synapses, despite normal dendritic complexity and intrinsic excitability. Moreover, recording of mPFC local field potentials (LFP) and unit spiking *in vivo* revealed increased activity in inhibitory neurons, reduced phase-locking to delta and theta oscillations and delayed phase-preference during locomotion. Excitatory neurons showed similar phase modulation changes at delta frequencies. Finally, pairwise correlations increased during immobility in KO mice. Thus, reduced synaptic inputs can yield perturbed temporal coordination of neuronal firing in cortical ensembles.

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352. Genetic Models for Autism Spectrum Disorders

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Topic: A.07. Developmental Disorders

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Medical Research Council (MRC MR/M006336/1)
Simons Initiative for the Developing Brain (SIDB)

Title: Cell type specific TRAP-seq identifies novel mechanisms in mouse models of autism

Authors: *E. K. OSTERWEIL, S. R. THOMSON, S. S. SEO, S. R. LOUROS, S. BARNES, M. MUSCAS;
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Abstract: Disrupted mRNA translation is a core contributor to neuropathology in multiple monogenic models of autism, including the *Fmr1*$^{-/y}$ mouse model of fragile X syndrome (FX). Phenotypes observed in multiple neural circuits in the *Fmr1*$^{-/y}$ brain are corrected by normalizing protein synthesis. However, the alternatively translated mRNAs that lead to disrupted function in these circuits have not been identified. To address this long-standing question, we are using cell type specific Translating Ribosome Affinity Purification and RNA sequencing (TRAP-seq) to interrogate mistranslating mRNAs in specific neuron populations in monogenic mouse models of autism. We recently used this strategy to examine CA1 pyramidal neurons in the *Fmr1*$^{-/y}$ hippocampus, which exhibit multiple electrophysiological phenotypes including exaggerated long-term synaptic depression downstream of $mGlu_5$ (mGluR-LTD). Our results identify a compensatory shift in the translating mRNA population in these neurons, including an alteration in the translation of muscarinic acetylcholine receptor 4 (M_4). Targeting this receptor with a positive allosteric modulator corrects biochemical, electrophysiological and behavioral phenotypes in the *Fmr1*$^{-/y}$ mouse. These results show TRAP-seq can identify previously overlooked changes that can be used to further understand disrupted neural function in specific circuits, and to identify novel therapeutic targets for FX.

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352. Genetic Models for Autism Spectrum Disorders

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Title: Impaired experience-dependent plasticity in anterior cingulate cortex in a mouse model of Angelman syndrome

Authors: *M. S. SIDOROV[1], H. KIM[1], M. ROUGIE[1], J. J. SIEGEL[2], J. P. GAVORNIK[3], B. D. PHILPOT[4];
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Abstract: The mouse visual system provides a model to study how experience modifies the brain. Mechanisms of experience-dependent plasticity have been well characterized in primary visual cortex (V1), including a form of potentiation driven by repeated presentations of a familiar visual sequence ("sequence plasticity"). The prefrontal anterior cingulate cortex (ACC) receives

input from visual cortex, yet little is known about how visual experience modifies ACC circuits. We found that ACC exhibits sequence plasticity, but the plasticity expresses as a change in response latency, rather than a change in response magnitude (as in V1). Sequence plasticity was absent in ACC, but not V1, in a mouse model of Angelman syndrome, a neurodevelopmental disorder associated with intellectual disability and autism-like features. Our results demonstrate that simple sensory stimuli can be used to reveal how experience functionally (or dysfunctionally) modifies higher-order prefrontal circuits, and suggest a divergence in how ACC and V1 encode familiarity.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

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Title: Disrupted experience-dependent changes in CA1 place cell information and hippocampal network coordination in a novel rat model of FXS

Authors: A. ASIMINAS[1], E. ALLISON[2], E. R. WOOD[2], ***P. C. KIND**[3];
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Abstract: Fragile X Syndrome is a common single gene cause of intellectual disability and Autism Spectrum Disorder. It is caused by silencing of the fragile X gene (*Fmr1*). Numerous studies have demonstrated abnormal synaptic plasticity and cognition in animal models of FXS.Two recent studies reported reduced spatial specificity (Arbab et al. Sci Rep 2018) and discoordinated discharge (Talbot et al. Neuron 2018) of hippocampal place cells in *Fmr1*KO mice. Furthermore, we have previously reported deficits in hippocampal plasticity and episodic memory in a rat model of FXS (Till et al. Hum Mol Genet 2015). In this study, we generated a novel rat model of FXS that contains a null mutation in exon 8 of the *Fmr1*gene on the Long-Evans Hooded background. We used *in-vivo*electrophysiology in awake, behaving rats to examine how loss of FMRP affects hippocampal spatial information processing correlated with

our observed deficits in episodic memory and hippocampal synaptic plasticity.We recorded from the CA1 in *Fmr1*KO and WT littermates over six 10 min exploration sessions in an initially novel environment - three sessions per day (ITI 10 min). Our recordings from pyramidal cells from 7 WT and 8 *Fmr1*KO rats revealedno significant differences between WT and *Fmr1*KO in firing rate, or in the number, size or in-field firing rate of their place fields. Firing rate maps also showed similar correlations between sessions for both genotypes, suggesting no reduction in place cell stability in the *Fmr1*KO rats. However, while on Day 1 the spatial information of place cell activity was similar between *Fmr1*KO and WT littermates, on Day 2 *Fmr1*KO rats showed significantly lower spatial information than WT. This finding suggests that the place cells of KO rats fail to show normal experience-dependent increase in spatial tuning over 24 hours. We also examined the temporal firing pattern (network state) of simultaneously recorded place cells in each session, and the recurrence of patterns between sessions. Our analyses indicate that *Fmr1 KO*rats exhibited abnormally high recurrence of network state between days compared to WT rats (who showed significantly less recurrence between days than within days). This abnormality was timescale-specific and relates to 40Hz gamma oscillation.In conclusion, unlike what was reported for *Fmr1*KO mice, in rats we found that hippocampal place cells from*Fmr1*KO rats show similar spatial firing properties as those from WT rats. However, they do show altered experience-dependent changes in spatial specificity and network coordination. In conclusion, the present study provides insight into altered circuit mechanisms that may contribute to the cognitive impairments observed in FXS.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

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Title: Mechanisms of atypical sensory information processing within the somatosensory cortex of an autism mouse model

Authors: *A. A. FRICK[1], A. A. BHASKARAN[2], G. BONY[2], K. LE CORF[2], R. PROVILLE[2]; [1]INSERM U1215, [2]Neurocentre Magendie, Bordeaux, France

Abstract: Atypical sensory information processing affects the vast majority of patients with fragile x syndrome (FXS) and autism spectrum disorder (ASD). Results from non-invasive imaging approaches in ASD patients led to the notion of the 'noisy brain' hypothesis of autism, but this has not been explored in preclinical models. We tested this theory in a mouse model for FXS/ASD by recording the activity of single layer 2/3 pyramidal neurons within the somatosensory cortex while stimulating the contralateral paw system. We found a complex phenotype composed of both cellular and circuit alterations including receptive field property changes, which negatively impacts on the precision of sensory information processing. Individual neurons displayed an intrinsic hyper-excitability phenotype, were spontaneously more active, and exhibited on average an increased sensory stimulus elicited action potential output and sub-threshold response. On the other hand, most of these parameters were much more variable compared to control mice, revealing a greater failure rate and baseline noise that reduced the signal-to-noise ratio of the sub-threshold response, and a broader time window for the onset of stimulus locked action potential firing. Furthermore, reorganization in the functional-structural connectivity of these neurons caused a larger percentage of neurons responding to both hind- and forepaw stimuli. Taken together, our data could explain a number of findings from the literature on ASD patients such as 'the noisy brain hypothesis', unreliable sensory information processing, alterations in the excitation-inhibition balance, and sensory hyper-/hyposensitivity. Interestingly, we were able to correct a number of these defects by local application of agonists of a particular ion channel type, suggesting this ion channel might be a suitable target for therapeutic correction of atypical sensory experience. At the behavioural level, we found evidence that this atypical sensory experience could also give rise to defects in sensorimotor gating behaviour.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

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Title: Visual recognition memory as a translational biomarker of genetically defined autism spectrum disorders

Authors: *P. S. B. FINNIE[1], L. J. PIERCE[2], E. S. KAPLAN[4], M. LEE[5], S. F. COOKE[6], C. A. NELSON[3], M. F. BEAR[1];
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Abstract: Neurodevelopmental disorders, such as autism spectrum disorders (ASDs) and co-morbid intellectual disability, are often diagnosed between 2-6 years of age, when children struggle in reaching developmental milestones despite typical progression during infancy. Hence, there is a well-recognized need for objective biomarkers that could reveal differences in brain function or plasticity prior to the emergence of diagnosable behavioral symptoms. One pervasive feature of ASD is hypo- or hyper-sensitivity to sensory stimulation, which may result in part from differences in experience-dependent habituation to familiar stimuli. Long-term habituation is a critically important but understudied form of learning that enables organisms to adaptively allocate neural resources to the detection of novelty. We have pinpointed the sites of synaptic modifications that underlie long-term habituation to familiar visual grating stimuli in mouse primary visual cortex, uncovered robust electrophysiological signatures for this plasticity, and demonstrated that these processes are disrupted by gene mutations linked to ASD (including tuberous sclerosis complex 2 heterozygosity, or *Tsc2*$^{+/-}$). The forms of long-term behavioral habituation and visual cortical plasticity we observe in mice have now been recapitulated in neurotypical human participants across days of exposure to visual grating stimuli. Thus we are leveraging visual recognition memory to establish a translational biomarker of genetically defined ASDs, with cortical microcircuitry that can be dissected via intersectional methods in transgenic mouse models.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

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Topic: A.07. Developmental Disorders

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Title: Critical period plasticity in fragile X syndrome

Authors: *M. M. HUNTSMAN[1], M. N. SVALINA[2], C. A. CEA-DEL RIO[3], A. F. NUNEZ-PARRA[4], D. RESTREPO[5];
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Abstract: In mouse models of Fragile X Syndrome (FXS), cellular and circuit hyperexcitability are a consequence of altered brain development. Differential circuit maturation leads to shifted time points for critical periods of synaptic plasticity across multiple brain regions and disruptions of the development of excitatory and inhibitory synaptic function are also observed both during development and into adulthood (Vislay et al., 2013)in FXS. However, little is known about how this hyperexcitable environment affects inhibitory synaptic plasticity. Our results demonstrate that the amygdala and somatosensory cortex of the *Fmr1*KO mouse model of FXS exhibits *increased* GABAergic spontaneous activity, a faulty mGluR-mediated inhibitory input and impaired inhibitory plasticity processes. In the amygdala, we observe an increase in synaptic plasticity between postnatal days (P) 14-16. This increased in plasticity in concomitant with an increase in synaptic inhibition. In the somatosensory cortex, we find that mGluR activation sensitivity in inhibitory interneurons is diminished in the *Fmr1*KO leading to both a decreased spontaneous inhibitory postsynaptic input to principal cells and also to a disrupted form of inhibitory long term depression (I-LTD). In cortical synapses, this I-LTD is dependent on the mobilization endocannabinoids (eCBs) and the presynaptic activation of PKA. Notably, these data suggest enhanced hyperexcitable phenotypes in FXS may be caused by an mGluR-mediated increased inhibitory drive of the network that in turn leads to a homeostatically counterbalanced modulation of cortical activity.

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Nanosymposium

352. Genetic Models for Autism Spectrum Disorders

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UC President's Postdoctoral Fellowship Program

Title: E-I ratio and circuit homeostasis in mouse models of autism

Authors: *D. E. FELDMAN, M. W. ANTOINE, T. LANGBERG, P. SCHNEPEL;
Molec & Cell Biology, and Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA

Abstract: Distinct genetic forms of autism have been proposed share a common circuit basis in increased excitation-inhibition (E-I) ratio in cerebral cortex, resulting in circuit hyperexcitability, excess spiking and degraded information processing. We tested this hypothesis by examining synapse physiology and sensory coding in somatosensory cortex (S1) of four mouse models of autism ($Fmr1^{-/y}$, $Cntnap2^{-/-}$, $16p11.2^{del/+}$, and $Tsc2^{+/-}$). All models had reduced inhibition, coupled with a smaller decrease in excitation, yielding an increase in E-I conductance ratio. However, synaptic depolarization was remarkably normal, as was whisker-evoked spiking *in vivo*. Modeling showed that E and I conductance changes were quantitatively matched to yield stable, not increased, synaptic depolarization. Quantitatively similar changes in E-I ratio occur in wild type mice during brief sensory deprivation, and constitute an endogenous homeostatic mechanism to stabilize cortical firing rate. Thus E-I ratio changes in these autism mouse models appear to represent a common homeostatic, compensatory response to circuit perturbation, rather than driving network hyperexcitability.

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Nanosymposium

353. Evolution and Development of Brain and Spinal Cord

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Topic: A.10. Development and Evolution

Support: NIH Grant R01 HD091846

Title: Variation and novelty in evolution: Novel genes continuously arise from non-coding regions, enable protein structural innovation and function in the brain

Authors: *V. LURIA[1], A. KARGER[2], J. W. CAIN[3], A. O'DONNELL-LURIA[4], M. KIRSCHNER[1];
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Abstract: How new protein-coding genes originate is a central, unsolved evolutionary question. Most genes were thought to arise by copying or transferring existing genes. Long thought impossible to arise from non-coding sequence, novel genes that arise *de novo* from genomic "junk" DNA or from long non-coding RNA have recently found in eukaryotic genomes. Novel

genes are taxon-restricted, being present in one or few species, and may encode structurally new proteins. Strikingly, novel genes are invariably expressed in the brain and germline. We initially found a taxon-restricted gene, *APCDD1*, and showed it functions in neurons and skin in humans and other chordates. To understand how novel genes appear, what proteins they make, what functions they have and what their general properties are, we combined mathematical, computational and experimental approaches. To evaluate how often may novel genes arise, we built a mathematical model based on gene and genome parameters and dynamic factors such as mutation. We found genomes should make many new genes and keep few. We computationally identified candidate novel genes in 25 eukaryotic genomes using phylostratigraphy and proteomics data and evaluated their predicted biophysical properties. Compared to ancient proteins, novel genes encode proteins that are shorter, fragile, disordered, promiscuous yet less prone to forming toxic prions or to aggregation. Third, we biophysically compared novel proteins to ancient proteins, we tested novel gene function *in vivo* in zebrafish brains using CRISPR inactivation, and we showed candidate novel genes are expressed in the human brain at multiple ages. We found that genomic sequence is turned over such that many novel genes arise continuously and encode short proteins, of which a small fraction perdures evolutionarily. The survivors encode proteins with distinct structural features and are expressed in the brain, suggesting genomes continually generate variation that enables new structures and functions, and is selected upon.

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Nanosymposium

353. Evolution and Development of Brain and Spinal Cord

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Title: Melanin-concentrating hormone peptidergic system comparative morphology between muroid species

Authors: *G. B. DINIZ[1], D. S. BATTAGELLO[1,2], P. M. CHERUBINI[1], J. D. REYES-MENDOZA[2], C. LUNA-ILLADES[2], M. O. KLEIN[1], L. C. MOTTA-TEIXEIRA[1,3], L. V. SITA[1], M. MIRANDA-ANAYA[4], T. MORALES[2], J. C. BITTENCOURT[1];
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Abstract: Melanin-concentrating hormone [MCH] is a conserved neuropeptide, predominantly located in the diencephalon of vertebrates, and associated with a wide range of functions. While functional studies have focused on the use of the traditional mouse laboratory model, critical gaps exist in our understanding of the morphology of the MCH system in this species. Even less is known about the non-traditional animal model *Neotomodon alstoni* (Mexican volcano mouse). A comparative morphological study among these rodents may, therefore, contribute to a better understanding of the evolution of the MCH peptidergic system. To this end, we employed diverse immunohistochemical protocols to identify key aspects of the MCH system, including its spatial relationship to another neurochemical population of the tuberal hypothalamus, the orexins. Three-dimensional reconstructions were also employed to convey a better sense of spatial distribution to these neurons. Our results show that the distribution of MCH neurons in all rodents studied follow a basic plan, but individual characteristics are found for each species, such as the preeminence of a periventricular group only in the rat, the lack of posterior groups in the mouse, and the extensive presence of MCH neurons in the anterior hypothalamic area of *Neotomodon*. Taken together, these data suggest a strong anatomical substrate for previously described functions of the MCH system, and that particular neurochemical and morphological features may have been determinant to species-specific phenotypes in rodent evolution.

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Topic: A.10. Development and Evolution

Support: Shriners Hospitals

Title: Cortical interlaminar astrocytes in mammalian evolution and development

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Abstract: Interlaminar astrocytes (ILA) are a subtype of astrocytes present in the cerebral cortex, with a soma in layer I and long interlaminar processes running perpendicularly to the pia into deeper cortical layers. We previously examined cerebral cortex from 46 species encompassing most orders of therian mammalians. We characterized ILA as pial and subpial (with different somatic morphology, position in layer I and presence across species), and we further described "rudimentary pial ILA" with short $GFAP^+$ processes that do not exit layer I, and "typical pial ILA", with longer $GFAP^+$ processes crossing layer I-II border. We found that ILA express astrocyte markers and do not express other cell-specific markers, and that they reach the highest values of density and complexity in Primates among all the species analyzed (Falcone et al, 19).
Here we performed a comparative study of ILA development in different species. ILA were known to be present and develop postnatally, but when exactly they appear during development is not known. We assayed ILA appearance and differentiation during development, by inspecting GFAP- and S100b-stained prenatal and postnatal brains of mouse (P1, P3, P5, P8, P12, P30, *n=3*), rhesus macaque (GD68, GD 84, GD93, GD109, GD123, GD150, *n=1;* and P15, P21, P30, P90, adult, *n=2*), chimpanzee (0y, *n=3*; 2y, 5y, 6y, 9y, 11y, *n=1*; and adult, *n=2*), and human (GW15, GW17, GW21, GW22.5, GW31.5, 2y, 5y, 10y, 15y, *n=1*; and adult, *n=3*). We found that they are present prenatally in macaque and human, and that they show an increasing linear density and morphological complexity throughout development, in all four species. Finally, we compared the expression of different markers in ILA across development (e.g. Pax6, Sox2, Hopx, Nestin, S100b, Glast, Aqp4, Ki67, and others) in mouse and macaque, and we showed protein expression differences and similarities among mouse rudimentary ILA and macaque typical ILA.
Data obtained from this project will shed light on the ILA nature and function in the evolution and development of the cerebral cortex.
Abbreviations: P= postnatal day; GD= gestation day; GW= gestation week; y= years

Disclosures: C. Falcone: None. **M. Wolf-Ochoa:** None. **S. Amina:** None. **T. Hong:** None. **G. Vakilzadeh:** None. **W.D. Hopkins:** None. **P.R. Hof:** None. **C. Sherwood:** None. **P.R. Manger:** None. **S.C. Noctor:** None. **V. Martínez Cerdeño:** None.

Nanosymposium

353. Evolution and Development of Brain and Spinal Cord

Location: Room S104

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 353.04

Topic: A.10. Development and Evolution

Support: JSPS KAKENHI 17K07428
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Takeda Science Foundation Research Grant 2018
The Naito Foundation Research Grant 2018

Title: Subplate neurons function as an organizer in neocortical development

Authors: *C. OHTAKA-MARUYAMA[1], N. KANEKO[1], A. FUJII[1], K. YURA[3], N. MAEDA[2]; [2]Neural Network Project, [1]Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan; [3]Dept. of Biol., Ochanomizu Univ., Tokyo, Japan

Abstract: The cerebral neocortex is responsible for higher order brain functions, such as cognition, memory and mental activity, in human. In the neocortex, billions of neurons are precisely arranged in an ordered 6-layered structure. This structure is formed by the sequential generation of neurons and their migration toward the brain surface in the fetal period. Various genes involved in mental disorders such as autism and schizophrenia are associated with defects in radial migration process, suggests that the elucidation of this mechanism will help in understanding these diseases. Subplate neurons are the first neurons born in the neocortex and work transiently during neocortical development. However, its role in corticogenesis has remained elusive. We have found that subplate neurons actively extend processes to form transient synapses on newly born multipolar migrating neurons and send signals to control their migration. This synaptic communication leads to switch from multipolar migration to locomotion. Subplate neurons have been known to guide thalamocortical afferents and help the first neural circuit formation in the cortex. Taken together, it is suggested that subplate neurons play as an organizer that arranges multiple processes such as production of neurons, migration, axon pathfinding and synaptogenesis that are proceeding at the same time during the limited developing period.

Disclosures: C. Ohtaka-Maruyama: None. **N. Kaneko:** None. **A. Fujii:** None. **K. Yura:** None.

Nanosymposium

353. Evolution and Development of Brain and Spinal Cord

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Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 353.05

Topic: A.10. Development and Evolution

Support: James S. McDonnell Foundation (Grant 220020516)

Title: Modelling the interaction of genetic and activity-dependent factors that shape the developing neocortex

Authors: *S. S. JAMES, S. P. WILSON;
Dept. of Psychology, The Univ. of Sheffield, Sheffield, United Kingdom

Abstract: Patterns of cortical arealization reflect developmental mechanisms that are influenced both by molecular signalling cues and by activity-dependent competitive interactions between thalamocortical axons. Computational modelling can help to tease apart the relative contribution of these factors in shaping the emergence of cortical fields. To this end, we have been developing a mathematical model of cortical arealization, which represents the following key assumptions, i) at each location on the cortical sheet the density of thalamo-cortical axon branching and the number of connections made with each cortical cell interact according to a positive feedback loop, ii) thalamocortical axons branch laterally at a rate determined by the availability of adjacent cortical neurons to form new connections, iii) different thalamic projections interact with fields of molecular signalling molecules with different magnitudes, resulting in a gradient ascent or descent in the branching density whose net effect is to robustly localise thalamic projections to specific cortical locations. Simulations of the model dynamics give rise to realistic patterns of cortical arealization, and provide a mechanistic account of the effects of modifying various molecular guidance cues, as established by gene knock-out experiments conducted in recent decades. Specifically, we recreate the classic result that ectopic expression of fibroblast growth factor 8 can lead to the duplication and the mirroring of the rodent primary visual cortex and somatosensory barrel field, and we recreate a range of modified barrel field topologies which have been shown to result from various manipulations of whisker stimuli. The model takes the form of a set of coupled reaction-diffusion systems (one for each thalamocortical projection), and extends an existing model by Karbowski & Ermentrout (2004; J Computational Neuroscience) by a) specifying two- (rather than one-) dimensional arealization patterns, and b) introducing an explicit diffusion-based competition between thalamic projections. A crucial feature of the formulation of the model is that information is exchanged only locally between immediate neighbours on a simulated lattice, hence the model accounts for cortical patterning as an emergent property of a small set of simple self-organising developmental processes

Disclosures: S.S. James: None. **S.P. Wilson:** None.

Nanosymposium

353. Evolution and Development of Brain and Spinal Cord

Location: Room S104

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 353.06

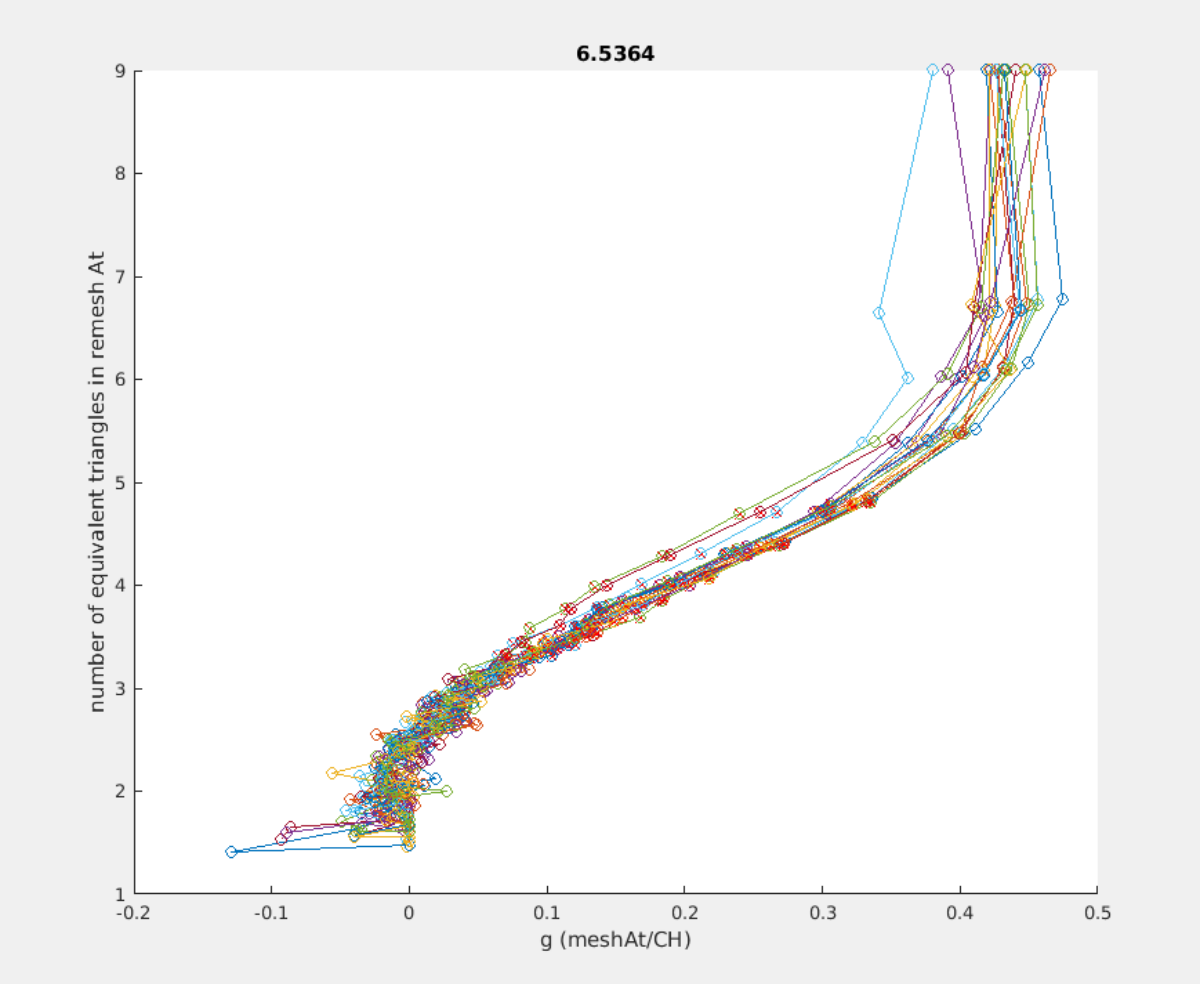
Topic: A.10. Development and Evolution

Support: Serrapilheira grant Serra-1709-16981
CNPq PQ 2017 312837/2017-8
Wellcome Trust 208940/Z/17/Z, 210109/Z/18/Z

Title: A multi-scale surface-preserving analysis of cortical morphology in a single cortex: Universality in the transition from fractal to lissencephalic

Authors: *B. MOTA[1], Y. WANG[2];
[1]Physics Inst., Univ. Federal do Rio De Janeiro, Rio de Janeiro, Brazil; [2]Sch. of Computing Sci., Newcastle University, United Kingdom

Abstract: We present a mathematical and computational procedure of coarse-graining a cortical surface in a way that preserves its topological integrity and non-self-intersecting nature. Each iteration of this procedure can thus be analysed using exactly the same methods we have previously applied to the entire cortex. We show how the scaling of the gyrification index is related to the fractal dimension of the cortex. This allows us to identify not only the scales in which the cortex is fractal, but also the so-called cutoffs, the scales at which it ceases to be fractal and becomes either smooth (for scales much smaller than the smallest gyri and sulci), or lissencephalic (for scales larger than the largest structures). This method probes cortical morphology in a way that neither reduces each cortex to a set of numbers (such as total area or average thickness), or to a detailed description of each sulci or gyri. Rather, it quantifies cortical morphology across different scales, which can then be used to characterize cortices of different species, and across development and aging, and across health and disease. We have previously demonstrated that folding in mammalian cerebral cortices follows a universal scaling law that can be derived from a simple physics model[1]. The same law also applies across healthy humans[2], and separately for different cortical lobes and regions in individual cortices[3]. With this method we can investigate if this universality is also present across different scales, and verify in a precise sense if a human cortex, over surface coarse-graining (i.e., ‘lowering resolution’), recapitulates the shapes of the cortices of less-gyrified mammals.



Number of surface triangles vs gyrification index for 10 human cortices during coarse-graining. Note the transition from a smooth regime (right) to a fractal regime (middle) to a lissencephalic regime (left)

[1] Mota B, Herculano-Houzel, S (2015) Science, 349 (6243) 74[2] Wang Y, Necus J, Kaiser M, Mota B (2016) PNAS 113 (45)[3] Wang Y, Necus J, Rodriguez, LR, Taylor, PN,, Mota B (2019) Comm. Bio. (Accepted for publication)

Disclosures: **B. Mota:** None. **Y. Wang:** None.

Nanosymposium

353. Evolution and Development of Brain and Spinal Cord

Location: Room S104

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 353.07

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFG Grant ZA 885/1-2

Title: Central canal formation and wiring of spinal circuit for left-right limb alternation depends on afadin function

Authors: *S. SKARLATOU[1,2], E. TOSCANO[3], C. MENDES[4], J. BOUVIER[5], N. ZAMPIERI[1,2];
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Abstract: Afadin, a scaffold protein controlling the activity of the nectin family of cell adhesion molecules, has been shown to regulate important morphogenetic processes during development. In the central nervous system, critical roles for afadin have been described in neuronal migration, axonal elongation and synapse formation (Okabe, et al., 2004, Takai et al., 2008, Rikitake et al, 2012, Beaudoin, et al., 2012). Recently, we found that afadin is required for migration and positioning of limb-innervating motor neurons in the spinal cord (Dewitz, et al., 2018). Here, we analyzed the consequences of afadin elimination in adult mice and observed a striking locomotor defect. Walking gait consisting of left-right limb alternation is substituted by synchronous activation of paired limbs characteristic of bound gait. In order to understand the mechanisms underlying this phenotype, we studied spinal cord development and the assembly of spinal motor circuits in afadin mutant mice. We found that afadin function at the neuroepithelium is important for central canal development. In its absence, two central canals are formed along the rostro-caudal axis of the spinal cord and, as a consequence, ephrin B3 expression at the midline is perturbed. Analysis of spinal premotor circuits revealed in addition aberrant patterns of connectivity in several spinal interneuron subtypes, highlighting their importance in the wiring of circuits controlling gait selection in mice.

Disclosures: S. Skarlatou: None. **E. Toscano:** None. **C. Mendes:** None. **J. Bouvier:** None. **N. Zampieri:** None.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.01

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

Support: Arizona Biomedical Research Commission
Arizona Alzheimer's Consortium
The Barrow Neurological Foundation

Title: The role of α7 and α7β2-containing nicotinic acetylcholine receptors (nAChRs) in mediating amyloid-beta induced basal forebrain cholinergic hyperexcitation and integration of spatial reference and working memory

Authors: *A. A. GEORGE[1], C. XAVIER-JACKSON[3], J. M. VIEIRA[4], M. T. GEE[5], H. A. BIMONTE-NELSON[4], R. J. LUKAS[6], P. WHITEAKER[2];
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Abstract: Alzheimer's disease (AD) is one of the most common causes of mental deterioration in the elderly. AD-related pathological hallmarks include extensive amyloid-beta (Aβ) deposition, aggregated neurofibrillary tangles, and early degeneration of basal forebrain cholinergic neurons (BFCNs). Aβ, a suspected etiopathogenic agent in AD, interacts with nicotinic acetylcholine receptors (nAChRs)containing α7 subunits, triggering hippocampal neuronal hyperexcitability. However, heteromeric α7β2 nAChRs are expressed preferentially in the basal forebrain and are sensitive to functional modulation by Aβ. In this study we used single-channel electrophysiology, whole-cell patch clamp recordings and Morris water maze behavioral testing to explore the functional relationship between Aβ and α7 and α7β2 nAChRs, the impact Aβ/nAChR interactions have on BFCN excitability, and the role α7 and/or α7β2nAChRs play in mediating Aβ-induced decline in cognitive function. We demonstrate that chronic administration of oligomeric Aβ(Aβo) activates both α7 and α7β2 nAChRs and preferentially enhances α7β2 nAChR single-channel open dwell-times (3-5 fold increase). These effects can be abrogated using the known nAChR antagonists MLA or mecamylamine. Using organotypic basal forebrain slice cultures prepared from ChAT-EGFP mice, we demonstrate that chronic Aβo exposure increases BFCN action potential firing rates in the medial septum and horizontal diagonal band (MSDB: 64 ± 8% and HDB: 25 ± 3.5%, respectively). Increased BFCN firing resulted from 1) attenuated afterhyperpolarization magnitude (MSDB, fAHP = 63 ± 2.5% and mAHP = 44 ± 6.5%; HDB, fAHP =58 ± 6.5% and mAHP = 55 ± 3.3%), 2) reduced latency to spike (MSDB = 43 ± 1.8% and HDB = 36 ± 2.1%) and 3) accelerated BFCN spike repolarization. These effects were absent in BFCNs recorded from the nucleus basalis (NB). Changes in BFCN excitability were normalized in organotypic slices incubated in Aβo with MLA or in organotypic preparations from β2 nAChR subunit knockout mice, suggesting that Aβo alters BFCN intrinsic excitability by interacting with α7 and β2-containing nAChRs. Lastly, we demonstrate that genetic deletion of the β2 nAChR subunit in APP/PS1 mice ameliorates spatial reference and working memory deficits associated with increased Aβo load. These mechanisms could be targeted for therapeutic intervention by manipulating Aβo/nAChR associations directly or through intervention of newly-defined downstream pathways altered by these interactions. This work was supported by the Arizona Biomedical Research Commission (AAG), the Arizona Alzheimer's Consortium (AAG) and the Barrow Neurological Foundation (AAG).

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Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.02

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

Support: Alzheimer's Association IIRG-09- 134220
Alzheimer's Association NIRG-14-321307
University of Catania intramural funds
PRIN 2010-JFYFY2
INRCA intramural funds

Title: Dissecting amyloid β physiological function at the synapse

Authors: *W. GULISANO[1], M. MELONE[2,3], C. RIPOLI[4,5], M. TROPEA[1], D. D. LI PUMA[4,5], S. GIUNTA[1], S. COCCO[4], D. MARCOTULLI[2], N. ORIGLIA[6], A. PALMERI[1], F. CONTI[2,3], C. GRASSI[4,5], D. PUZZO[1,7];
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Abstract: The increase of oligomeric amyloid-beta (oAβ) is considered one of the earliest events in Alzheimer's disease (AD) pathophysiology, leading to synaptic dysfunction and memory loss. However, failure of anti-Aβ therapies and growing evidences on Aβ physiological function in the healthy brain has prompted the neuroscience community to re-evaluate the Amyloid Cascade Hypothesis of AD. It has been previously demonstrated that $oA\beta_{42}$ is needed for synaptic plasticity and memory and, when at picomolar concentrations, resembling the physiological content in the brain, it enhances long-term potentiation and memory. Here, we aimed to investigate the pre- and post-synaptic mechanisms underlying the neuromodulatory role of picomolar $oA\beta_{42}$ at the synapse in male and female mice.We first studied the effect of 200 pM $oA\beta_{42}$ on glutamatergic basal synaptic transmission through dual patch-clamp whole-cell recordings of CA1 pyramidal neurons. We found that $oA\beta_{42}$ enhanced neurotransmitter release as indicated by the increase of miniature excitatory postsynaptic current frequency and the decrease of paired-pulse facilitation. Consistently, electron microscopy performed on hippocampal slices used for electrophysiological recordings showed a higher amount of docked vesicles in axon terminals after 200 pM $oA\beta_{42}$ treatment. $oA\beta_{42}$ also produced postsynaptic changes as suggested by an increased length of postsynaptic density, accompanied by a higher expression of plasticity-related proteins such as phospho-CREB (Ser133), phospho-CaMKII

(Thr286), and BDNF. These changes resulted in the conversion of early into late long-term potentiation and of short- into long-term memory through the nitric oxide/cGMP/protein kinase G intracellular cascade. Finally, we have demonstrated that the o$A\beta_{42}$-induced effects were present upon extracellular but not intracellular application of the peptide and depended upon α7 nicotinic acetylcholine receptors. These findings clarified some aspects concerning the physiological role of o$A\beta_{42}$ on synaptic function and memory formation and provide fundamentals for investigating the pathological effects of Aβ occurring when it abnormally increases in the brain of AD patients.

Disclosures: W. Gulisano: None. **M. Melone:** None. **C. Ripoli:** None. **D.D. Li Puma:** None. **S. Giunta:** None. **M. Tropea:** None. **D. Marcotulli:** None. **N. Origlia:** None. **F. Conti:** None. **C. Grassi:** None. **D. Puzzo:** None. **A. Palmeri:** None. **S. Cocco:** None.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.03

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

Title: Examining the role of n-terminal abeta fragments in mitigating full-length abeta-induced phenotypic alterations in primary astrocytes and microglia

Authors: *M. J. LANTZ, R. A. NICHOLS;
Cell and Mol. Biol., Univ. of Hawaii, Honolulu, HI

Abstract: Examining the Role of N-Terminal Aβ Fragments in Mitigating Full-Length Aβ-Induced Phenotypic Alterations in Primary Astrocytes And Microglia
A hallmark of Alzheimer’s disease (AD) is the accumulation of soluble, oligomeric beta amyloid (Aβ) peptide causing astrocytes and microglia to undergo a phenotypic shift from a normal resting state in which they provide many diverse neuromodulatory functions, to a reactive phenotype that exacerbates neuronal death.
Our lab previously showed the endogenous N-terminal fragment of Aβ, termed N-Aβ fragment, and its critical hexapeptide core sequence N-Aβcore (collectively termed N-Aβ fragments), protect against full-length Aβ-induced cellular neurotoxicity and synaptic dysfunction in neurons as well as behavioral dysfunction in whole animals. Recently, we discovered these N-Aβ fragments also mitigate Aβ-induced cellular toxicity in astrocytes and microglia. Our objective was to investigate whether the N-Aβ fragments could modulate the phenotypic state of astrocytes and microglia in a pro-inflammatory environment. Primary cortical neuronal/glia cultures, cortical glia cultures or hippocampal slice cultures, were treated with culture media (control) or 1μM Aβ, N-Aβ fragment, or N-Aβcore, alone or in combination, in media over the course of 1-5 days prior to examining alterations in cell- and phenotype-specific proteins expressed in

astrocytes and microglia by immunoblot and immunocytochemistry. Additionally, changes in intracellular calcium concentrations ($[Ca^{2+}]_i$) were measured in primary glial cultures perfused with 1μM Aβ, N-Aβ fragment, or N-Aβcore treatments, as elevated levels of Aβ disrupt calcium homeostasis in glia, producing a prolonged increase in $[Ca^{2+}]_i$ that evoke persistent activation of many cellular pathways. Here, we show the N-Aβ fragments induce weaker $[Ca^{2+}]_i$ responses in glial cells than full-length Aβ, indicating these fragments may induce differential signaling in primary astrocytes and microglia than full-length Aβ. In addition, Aβ treatment induces a rapid phenotypic shift in primary astrocytes and microglia, consistent with previous evidence. We expect co-treatments with the N-Aβ fragments will modulate this phenotypic shift in primary astrocytes and microglia.
In conclusion, the findings of this study provide insight into the function of the N-Aβ fragments in mitigating the phenotypic shift induced by full-length Aβ. These results provide a basis for developing novel approaches for maintaining the neurosupportive role of astrocytes and microglia in AD by limiting their persistent activation to a pro-inflammatory, cytotoxic phenotype induced by full-length Aβ.

Disclosures: **M.J. Lantz:** None. **R.A. Nichols:** None.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.04

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

Support: NIH R01 AG050658

Title: Microtubule dynamics at synaptic contacts are modulated by neuronal activity and affected by oligomeric Ab_{1-42}

Authors: X. QU[1], A. KUMAR[1], H. BLOCKUS[1], C. WAITES[1], ***F. BARTOLINI**[2];
[2]Pathology & Cell Biol., [1]Columbia Univ., New York, NY

Abstract: Emerging studies from several groups have indicated that dynamic microtubules (MTs), in addition to modified MTs, play key roles in neuronal function. In addition, synaptic biphasic fluctuations of MT instability/stability and tubulin post-translational modifications (PTMs) are associated with memory formation and are disrupted in aging, indicating a primary role for the regulation of MT dynamics and tubulin PTMs in the maintenance of synaptic plasticity. In support of this model, we recently found that stabilization of dynamic MTs and induction of tubulin PTMs by the formin mDia1 contribute to oligomeric Aβ1-42 synaptotoxicity, and inhibition of MT dynamics alone is sufficient to promote tau hyperphosphorylation and tau dependent synaptotoxicity (Qu et al., J Cell Biol, 2017). To test

whether these changes occur at synapses and are directly responsible for synapse loss, we have further developed microscopy assays that measure MT invasions into dendritic spines and MT contacts with single presynaptic boutons of hippocampal neurons in culture. We found that dynamic MT plus ends preferentially grow near presynaptic boutons, and rescue/nucleation at boutons is enhanced by neurotransmitter release or when neurons are challenged with oligomeric $A\beta_{1-42}$(Aβ), an activity mediated by tau. Aβ also acutely affected the fraction of spines invaded by MTs, which appeared to be the most resistant to injury-dependent structural plasticity. Our data underscore the existence of a previously uncharacterized pool of presynaptic dynamic MTs that respond to neurotransmission and excitotoxicity, and reveal a function for spine-invading MTs in conferring resistance to pruning.

Disclosures: **X. Qu:** None. **A. Kumar:** None. **H. Blockus:** None. **C. Waites:** None. **F. Bartolini:** None.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

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Presentation Number: 354.05

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

Support: NIH Grant AG030142
NCI CCSG P30 CA060553
NIH 1S10OD010398-01

Title: The effect of a calcium channel modulator on β-secretase elevation in Alzheimer's disease

Authors: ***K. R. SADLEIR**[1], J. POPOVIC[1], A. SOMASUNDARAM[2], H. DO[3], C. T. REIDL[3], W. ZHU[3], M. PRAKRIYA[2], R. B. SILVERMAN[3], R. VASSAR[1];
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Abstract: BACE1 is the β-secretase enzyme that initiates Aβ production and is a prime therapeutic target for Alzheimer’s disease (AD). Drugs that inhibit BACE1 enzyme activity are in clinical trials for AD, but early termination of a recent trial raises concerns regarding safety and efficacy of these agents. Animal studies suggest that BACE1 inhibition may cause multiple neurological side effects. Thus, it is crucial to develop alternative therapeutic strategies that reduce BACE1 cleavage of APP without impairing essential BACE1 functions. We have shown that global BACE1 protein levels are markedly elevated in APP transgenic mouse and AD brains. Elevated BACE1 is concentrated within dystrophic axons surrounding amyloid plaques, and is associated with increased generation of BACE1-cleaved APP fragments and Aβ42. Our preliminary results show that Aβ elevates resting $[Ca^{2+}]i$ in primary neurons via calcium

channels. Peri-plaque dystrophic axons in 5XFAD mice also show elevated resting [Ca^{2+}]i and disrupted microtubules. We hypothesize a feed-forward mechanism in which plaque-associated Aβ causes axonal dystrophy, BACE1 accumulation, and accelerated Aβ generation that drives amyloid progression.
Our goal is to understand the mechanisms of dystrophy formation and target these pathways as a potential therapeutic approach. We are focusing on mitigating the increased resting calcium in dystrophic axons. To do this, we treated 5XFAD mice with pregabalin, which interacts with the α2-δ2 subunit of voltage gated calcium channels, lowering presynaptic resting calcium. At five months of age, brains from 5XFAD or non-transgenic littermates treated with pregabalin or vehicle were stained with Lamp1 and BACE1 to mark dystrophic neurites, and thiazine red to mark plaques. From these images, neuritic dystrophy and amyloid deposition were quantified. In addition, BACE1 and amyloid levels were measured using biochemical methods. To assess changes in calcium concentration, we measured phosphorylation of CaMKII and its downstream target synapsin by immunoblot and immunofluorescence. In addition, we measured [Ca^{2+}]i in dystrophic neurites and neurons by multiphoton imaging of live brain slices of pregabalin and vehicle treated 5XFAD mice who underwent postnatal day 0 intracerebral injections of AAV expressing the commonly used calcium sensor proteins GCaMP6f, or a ratiometric calcium sensor Twitch2B. We hypothesize that the pregabalin treated mice will have reduced peri-plaque dystrophic axons and lowered resting calcium compared to vehicle treated mice.

Disclosures: **K.R. Sadleir:** A. Employment/Salary (full or part-time):; Northwestern University. **J. Popovic:** A. Employment/Salary (full or part-time):; Northwestern University. **A. Somasundaram:** None. **H. Do:** A. Employment/Salary (full or part-time):; Northwestern University. **C.T. Reidl:** A. Employment/Salary (full or part-time):; Northwestern University. **W. Zhu:** A. Employment/Salary (full or part-time):; Northwestern University. **M. Prakriya:** A. Employment/Salary (full or part-time):; Northwestern University. **R.B. Silverman:** A. Employment/Salary (full or part-time):; Northwestern University. **R. Vassar:** A. Employment/Salary (full or part-time):; Northwestern University.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

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Presentation Number: 354.06

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

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Title: Amyloid precursor protein phosphorylation at distinct residues regulates homeostatic synaptic plasticity

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Abstract: Alzheimer's disease (AD), the most common neurodegenerative disorder, is thought to be initiated by the accumulation of amyloid beta (Aβ), a proteolytic cleavage product of amyloid precursor protein (APP). We previously identified polo-like kinase (Plk) 2, a mediator of homeostatic synaptic plasticity in response to hyperexcitation, as a novel molecular mechanism underlying synaptic activity-dependent production of Aβ. We found that two sites in the APP cytosolic tail (Thr668/Ser675), which have been shown to be elevated in AD patients' brains (Lee et al., JRC 2003), are directly phosphorylated by Plk2 to regulate APP internalization as well as amyloidogenic processing. Here, we aimed to test the hypothesis that phosphorylation of APP by Plk2 at these residues governs the interconnected processes of APP internalization, production of Aβ, and synaptic removal of AMPARs under conditions of homeostatic synaptic plasticity. Hippocampal cultured primary rat neurons at DIV 19-20 were transfected with constructs expressing either APP wild-type (WT) or APP-2A-HSP (Thr668/Ser675 sites mutated to nonphosphorylatable alanines). At DIV 20-21, neurons were treated with control vehicle or 100 μM picrotoxin (PTX), a $GABA_A$ receptor antagonist, to induce chronic hyperactivity for 24 hours, followed by patch clamp electrophysiological analyses. AMPAR miniature excitatory postsynaptic currents (mEPSCs) were recorded in the presence of 1 μm tetrodotoxin (TTX) and 25 μM bicuculline methobromide (BMR), and morphological analysis of neuronal population subtypes was performed as described (Lee et al., Neuron 2013). In morphologically identified pyramidal neurons transfected with APP-2A-HSP and treated with vehicle, mEPSCs peak amplitude was significantly larger than in neurons transfected with APP-WT and treated with vehicle. Paradoxically, PTX treatment significantly increased mEPSC peak amplitude in APP-WT neurons compared to vehicle. However, PTX treatment did not alter the mEPSC amplitude of neurons transfected with APP-2A-HSP. No change was observed in mEPSC frequency for all conditions. Spontaneous paroxysmal depolarizing shift frequency significantly decreased with neurons transfected with APP-2A-HSP vs. APP WT treated with vehicle but not PTX, suggesting neurons transfected with the mutant APP are uncoupled from the network. We propose that the lack of effect observed for PTX on the mutant form of APP is caused by the silencing of the network stimulation of neurons containing mutant APP.

Disclosures: S.N. Garcia DuBar: None. **D.T. Pak:** None. **S. Vicini:** None.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.07

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

Support: Italian Ministry of Education University and Research: 2015W729WH_005
Università Cattolica intramural grants

Title: Amyloid-β-dependent impairment of adult hippocampal neurogenesis in a mouse model of recurrent herpes simplex virus type-1 infection

Authors: *R. PIACENTINI[1,2], D. D. LI PUMA[1,2], L. LEONE[1,2], K. GIRONI[1], M. E. MARCOCCI[3], G. DE CHIARA[4], A. T. PALAMARA[3,5], C. GRASSI[1,2];
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Abstract: Defects in adult hippocampal neurogenesis have been proposed to play a crucial role in cognitive dysfunction associated with Alzheimer's disease (AD). However, if amyloid-β protein (Aβ) affects neurogenesis is still unclear, likely due to the use of different experimental conditions (e.g. cellular/animal models, Aβ isoforms, concentrations, and aggregation profiles) leading to conflicting results. Here we investigated the effects of Aβ on adult hippocampal neurogenesis by using an experimental paradigm of Herpes Simplex Virus type-1 (HSV-1) infection of neural stem/progenitor cells (NSCs), that we previously reported to trigger Amyloid Precursor Protein (APP) cleavage and intracellular Aβ accumulation in neuronal cells (Piacentini et al., 2011, 2015). Cultured NSCs were highly permissive to HSV-1 and, once infected, they accumulated Aβ and exhibited reduced proliferation (-30% *vs*. mock-infected cells, $p<0.05$, assessed by BrdU incorporation, Ki67 immunoreactivity and Sox2 mRNA expression) and impaired neuronal differentiation (-35%; $p<0.01$) in favor of glial phenotype (evaluated by immunoreactivity for the neuronal marker MAP2, the glial marker GFAP and the expression of the pro-neuronal genes Mash-1 and NeuroD1). The effects of HSV-1 on cultured NSCs were due to Aβ accumulation. Indeed, they were reverted by the presence of either β/γ-secretase inhibitors preventing Aβ production or the 4G8 antibody counteracting the action of intracellular Aβ, in infected cells. Moreover, extracellular oligomeric Aβ42 (200 nM), able to enter NSCs, mimicked the effects of HSV-1. Impaired adult neurogenesis was also observed in the hippocampal dentate gyrus of an *in vivo* model of recurrent HSV-1 infections, that we recently set up and characterized (De Chiara et al., 2019). Specifically, immunofluorescence experiments revealed a reduction of $BrdU^+$ NSCs in the subgranular zone (SGZ) and of cells double-labelled for BrdU and the immature neuronal marker doublecortin (DCX) in the granule cell layer of HSV-1- *vs*. mock-infected mice (-28% and -41%, respectively, $p<0.01$). Western blot experiments also revealed a reduction of NeuroD1 and DCX protein expression at hippocampal level (-40% and -47%, respectively, *vs*. mock; $p<0.05$). Impaired neurogenesis correlated with Aβ accumulation in $nestin^+$ cells of the SGZ of infected mice. In fact, it was not detectable in infected $APP^{-/-}$ mice unable to produce Aβ, despite the presence of HSV-1 in their brains. Overall, these results

suggest that HSV-1-induced Aβ accumulation impairs adult hippocampal neurogenesis, likely contributing to AD-like phenotype occurring in mice subjected to multiple HSV-1 reactivations.

Disclosures: **R. Piacentini:** None. **D.D. Li Puma:** None. **L. Leone:** None. **K. Gironi:** None. **M.E. Marcocci:** None. **G. De Chiara:** None. **A.T. Palamara:** None. **C. Grassi:** None.

Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.08

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

Support: PRIN 2017A9MK4R_004

Title: A mouse model of recurrent herpes simplex virus type-1 infections exhibits synaptic dysfunction and memory impairment reminiscent of Alzheimer’s disease phenotype

Authors: *D. D. LI PUMA[1,2], R. PIACENTINI[1,2], S. COCCO[1], M. RINAUDO[1], G. DE CHIARA[3], A. T. PALAMARA[4,5], C. GRASSI[1,2];
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Abstract: Epidemiological and experimental evidence suggests that Herpes Simplex virus type-1 (HSV-1) infection is a risk factor for Alzheimer’s disease (AD). We recently set up an *in vivo* model (female BALB/c mice) of multiple HSV-1 reactivations exhibiting typical AD hallmarks, including accumulation of amyloid-β protein, tau hyperphosphorylation and neuroinflammation in several brain areas (De Chiara et al., 2019).
Here we used a similar experimental paradigm to investigate the impact of virus infection on synaptic function and memory in 5-month-old male C57/bl6 mice infected with HSV-1 and subjected to multiple reactivations in the brain.
Results showed that synaptic plasticity at the hippocampal CA3-CA1 synapse, assessed by long-term potentiation protocol, was significantly reduced in brain slices from HSV-1-infected mice compared to mock-infected ones: the fEPSP amplitude was 58.2±7.9% of the baseline (n=16 slices from 5 mice) *vs*. 97.6±10.8% (n=17 slices from 7 mice, $p<0.05$), respectively. The HSV-1-infected mice also exhibited memory impairment, assessed by the novel object recognition (NOR) and fear conditioning tests. Specifically, in the NOR paradigm the preference index was 57.5±2.8% (n=14) *vs*. 65.8±2.4% (n=16) in HSV-1- and mock-infected mice, respectively ($p<0.05$). The contextual fear memory was also reduced in infected mice: freezing behavior was

30.4±3.0% (n=14) in HSV-1-infected mice and 41.9±3.1% (n=15) in controls ($p<0.05$). Moreover, Western blot and immunohistochemistry experiments revealed a significant reduction of synapsin and synaptophysin protein levels in hippocampi of infected C57/bl6 mice (-50% [n=7 for each condition] and -30% [n=7 for mock and n=6 for HSV-1] respectively, *vs.* mock, $p<0.05$). Functional, behavioral and molecular alterations correlated with the presence of HSV-1 in mice brains, assessed by real time PCR and immunohistochemistry for the early viral protein ICP4.
Collectively, our results suggest that HSV-1 reactivations into the brain induce an AD-like phenotype consisting in synaptic plasticity and memory impairment in C57/bl6 mice. These findings further support the HSV-1 role in AD pathophysiology.

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Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.09

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

Title: Glucocorticoid receptor modulation alters dendritic spine density and microglia activity in an animal model of Alzheimer's disease

Authors: *M. PEDRAZZOLI[1], M. LOSURDO[4], G. PAOLONE[2], M. MEDELIN[1], L. JAUPAJ[1], B. CISTERNA[1], A. SLANZI[3], M. MALATESTA[1], S. COCO[4], M. BUFFELLI[1]; [1]Dept. of Neuroscience, Biomedicine And Movement Sci., [2]Dept. of Diagnostics and Publ. Hlth., [3]Dept. of Med., Univ. of Verona, Verona, Italy; [4]Dept. of Med. and Surgery, Univ. of Milano Bicocca, Monza, Italy

Abstract: Chronic exposure to high dose of glucocorticoids (GC) is a key risk factor for the development of Alzheimer’s disease (AD). Furthermore, hyper-activation of glucocorticoids receptors (GR) induces, in brain, alterations comparable to those produced by AD. In 3xTg-AD mice (a model of AD), GC induces the increasing production of Aβ40, Aβ42 and Tau total, the most important and typical hallmarks of this dementia. Two of the key roles of GC in brain are the regulation of dendritic spine turnover and the inflammation state, two phenomena strongly altered in AD. Despite extensive efforts, the molecular mechanisms driving this detrimental alteration have not been unveiled as yet. Here, we evaluated the role of GR agonists and antagonists on dendritic spine plasticity and microglia activation in CA1 region of hippocampus of 3xTg-AD mice. Thus, using an innovative combined Golgi Cox and immunofluorescence technique, we found that 5 days of treatment with 8mg/kg of dexamethasone, an agonist of GR, was able to vigorously reduce dendritic spine density in CA1 region of 3xTg-AD mice, both at 6

and 10 months of age and induced proliferation and activation of microglia. On the contrary, the treatment with 20mg/kg of mifepristone, an antagonist of GR, strongly enhanced dendritic spine density in CA1 region, at both ages, results confirmed also by electron microscopy analyses. Moreover, the antagonist was able to improve the 3xTg-AD mice performance in Y-maze task at 10 months of ages and the proliferation of microglia, but it was not able to reduce the activation of microglia. We speculated that these apparently ambiguous results could be explained by the well-known biphasic behavior of GC in brain. Additionally, *in vitro* experiments, using immunofluorescence and immunoblotting techniques, revealed that dexamethasone, clearly, induced activation of microglia in *vitro*, a result never described before. On the contrary, mifepristone promoted both activation and inhibition of microglia inflammatory state, suggesting the existence of a biphasic behavior of GC also on inflammation regulation. In conclusion, my data demonstrates that stress induced by dexamethasone exacerbate AD and promote a more rapid progression of the pathology. Consequently, the use of antagonist, like mifepristone, could represent a promising therapeutic strategy to delay the onset and slow down the progression of AD.

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Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

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Presentation Number: 354.10

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

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Title: Fluoxetine and Vortioxetine reverse depressive-like phenotype and memory deficits induced by $A\beta_{-42}$ oligomers in mice: A key role of transforming growth factor-β1

Authors: S. A. TORRISI[1], F. GERACI[1], M. TROPEA[1], M. GRASSO[3], G. CARUSO[3], A. FIDILIO[4], N. MUSSO[1], G. SANFILIPPO[1], F. TASCEDDA[5], A. PALMERI[1], S. SALOMONE[1], F. DRAGO[6], D. PUZZO[2], G. LEGGIO[6], ***F. CARACI**[4];
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Abstract: Depression is a risk factor for the development of Alzheimer's disease (AD), and the presence of depressive symptoms significantly increases the conversion of Mild Cognitive Impairment (MCI) into AD. Deficit of Transforming-Growth-Factor-β1 (TGF-β1) signaling is a common pathophysiological event both in depression and AD (Caraci et al., Pharmacol Res 130, 2018). TGF-β1 is an anti-inflammatory cytokine that exerts neuroprotective effects against Aβ-induced neurodegeneration and it has a key role in memory formation and synaptic plasticity. TGF-β1 plasma levels are reduced in major depressed patients (MDD) and correlate with depression severity. A long-term treatment with antidepressants reduces the risk to develop AD and different second-generation antidepressants are currently studied for their neuroprotective properties in AD. SSRIs, such as fluoxetine, increase the release of TGF-β1 from astrocytes and exert relevant neuroprotective effects in experimental models of AD. We tested the SSRI fluoxetine and the new multimodal antidepressant vortioxetine for their ability to prevent memory deficits and depressive-like phenotype induced by intracerebroventricular injection of amyloid-β (1-42) ($A\beta_{1-42}$) oligomers in 2 month-old C57BL/6 mice. Starting from 7 days before Aβ injection, fluoxetine (10 mg/kg) and vortioxetine (5 and 10 mg/kg) were intraperitoneally injected daily, for 24 days. Chronic treatment with fluoxetine and vortioxetine (both at the dose of 10 mg/kg) was able to rescue the loss of memory assessed 14 days after Aβ injection by the passive avoidance task and the object recognition test. Both antidepressants reversed the increase in immobility time detected 19 days after Aβ injection by forced swim test. Vortioxetine exerted significant antidepressant effects also at the dose of 5 mg/kg. A significant deficit of TGF-β1, paralleling memory deficits and depressive-like phenotype, was found in the hippocampus of Aβ-injected mice. Fluoxetine and vortioxetine completely rescued hippocampal TGF-β1 levels in Aβ-injected mice. This is the first evidence that a chronic treatment with fluoxetine or vortioxetine can prevent both cognitive deficits and depressive-like phenotype in a non-transgenic animal model of AD with a key contribute of TGF-β1.

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354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.11

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

Support: NIHR01AG0442603

Title: *In vivo* mitochondrial oxidative stress in a mouse model of Alzheimer's disease

Authors: *M. CALVO RODRIGUEZ, A. C. SNYDER, S. S. HOU, F. ZHANYUN, B. J. BACSKAI;
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Abstract: Alzheimer’s disease (AD) is characterized by the deposition of the amyloid beta (Aβ) peptide in extracellular senile plaques, the accumulation of microtubule-associated protein tau in intraneuronal neurofibrillary tangles and neuronal cell loss. Although the cellular and molecular mechanisms underlying the disease are still unknown, Aβ oligomers (Aβo) surrounding plaques are thought to be the most toxic species of Aβ and upstream of tau aggregation. Among the downstream neurotoxic effects of Aβo, mitochondrial dysfunction has been proposed as an early pathogenic event. An immediate consequence of mitochondrial dysfunction is the increase of reactive oxidative species (ROS), which cause oxidative damage to DNA, RNA, proteins and lipids, ultimately leading to cell death. Interestingly, mitochondrial abnormalities have been found in neurons and astrocytes in the AD brain, suggesting elevated ROS levels in both cell types.
Expressing a mitochondria-targeted ratiometric roGFP-based indicator of oxidative stress in neurons and astrocytes and imaging with intravital multiphoton microscopy, we measured oxidative stress levels in mitochondria in the APP/PS1 transgenic mouse model of AD, which exhibits amyloid plaque deposition as early as 4 month of age. We observed an increase in the mitochondrial oxidative stress levels in APP/PS1 mice, compared to wild-type (Wt) mice. In addition, direct topical application of Aβo-enriched transgenic conditioned media (TgCM, obtained from 14 DIV neurons prepared from Tg2576 mouse embryos) to the living health brain of Wt C57Bl/6 mice increased oxidative stress levels in individual mitochondria, whereas conditioned media obtained from the Wt littermates neurons (WtCM) or Aβo-depleted conditioned media had no effect. These results demonstrate increased mitochondrial oxidative stress levels in AD transgenic mice, which are, at least partially, due to soluble Aβo. Moreover, these tools will enable testing therapeutics directed at reducing the mitochondrial oxidative stress associated to AD *in vivo*.

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Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

Time: Monday, October 21, 2019, 1:00 PM - 4:30 PM

Presentation Number: 354.12

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

Support: Keck School of Medicine

Title: Cyclic-AMP prevents beta-amyloid internalization via 67kDa laminin receptor and causes signaling for neuroprotection against beta-amyloid toxicity

Authors: *R. GOPALAKRISHNA[1], C. LIN[1], S. YANG[1], C. LE[1], M. S. KINDY[2], N. R. BHAT[3];
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Abstract: Oligomers of β-amyloid (Aβ) internalize into neurons by binding to various cell-surface receptors and causing neuronal death. Others have shown that Aβ binds to 67kDa laminin receptor (67LR) either directly or indirectly through initial association with prion proteins, and subsequently internalizing into neurons to cause death. The mechanisms by which Aβ is internalized and cause cell death are unknown. Cyclic-AMP is known to counteract Aβ and protects neurons from death. Currently cyclic nucleotide phosphodiesterase inhibitors that elevate intracellular cAMP are in clinical trials for the treatment of Alzheimer's disease. The mechanism by which cAMP protects neurons from Aβ-induced cell death remains to be determined. In our current study, we have found that nanomolar concentrations of the Aβ(25-35) peptide, not the scrambled Aβ(25-35) control, induced death in Neuroscreen-1 (NS-1) cells as measured by the reduction of thiazolyl blue tetrazolium bromide. Anti-67LR-blocking antibody substantially prevented the cell death induced by Aβ peptide. Correspondingly, this antibody also decreased internalization of fluorescently labeled Aβ(1-42) suggesting that 67LR is a major receptor that mediates Aβ-induced cell death. A pretreatment of NS-1 cells for one hour with dibutyryl-cAMP, a cell-permeable analogue of cAMP, forskolin, an activator of adenylyl cyclase, or rolipram, a cyclic nucleotide phosphodiesterase inhibitor led to a decrease in Aβ-induced cell death as well as a decrease in the internalization of fluorescently labeled Aβ(1-42). Under these conditions, cAMP-elevating agents induced internalization of 67LR. This suggests that there is a decrease in cell-surface levels of 67LR, reducing the receptor availability for the internalization of Aβ and thereby preventing cell death. We treated NS-1 cells with Aβ first for 1 h, and then treated them with cAMP-elevating agents to determine whether they protect cells from death even after internalization of Aβ. This order of treatment also protected cells from death induced by Aβ although to a lower extent. Aβ decreased phosphorylation of cyclic-AMP response element-binding protein (CREB) in response to NGF treatment. A pretreatment with cAMP-elevating agents restored this phosphorylation. Conceivably, cAMP protects neuronal cells from Aβ-induced toxicity by decreasing the cell-surface 67LR, a receptor for Aβ internalization as well as by inducing the downstream signaling for neuroprotection by enhancing phosphorylation of CREB. The drugs that elevate intracellular cAMP may have a therapeutic role in the prevention and treatment of Alzheimer's disease.

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Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

Location: Room S103

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Presentation Number: 354.13

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

Support: NIH Grant 800105

Title: Histone acetyltransferase Tip60 mediated rescue in amyloid-β-induced Alzheimer's disease neuropathology

Authors: *H. ZHANG, B. KARISETTY, S. MORTAZAVI, S. MANDLOI, S. PERVEZ, F. ELEFANT;
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Abstract: Epigenetic mechanisms such as histone acetylation modifications play a crucial role in Alzheimer’s disease (AD) pathogenesis. Under AD conditions, the proper histone acetylation homeostasis is disrupted. Pilot studies in our lab have provided solid evidence of neuroprotective function of Tip60 histone acetyltransferase against amyloid precursor protein (APP)-induced AD pathologies. Abnormal APP processing generates neurotoxic amyloid-β (Aβ), however, whether Tip60 can also protect against Aβ-induced neurodegeneration remains to be explored. Here we utilize a double transgenic fly model (Aβ42; Tip60) to increase Tip60 levels in the brain of an AD associated Aβ42 induced neurodegenerative *Drosophila* model. We show that increased Tip60 levels in the Aβ fly brain sustainably suppresses histone deacetylases 1/2 (HDAC1/2) expression and maintains appropriate histone acetylation levels throughout development. This restored epigenetic homeostasis leads to an efficient amelioration of direct Aβ-induced pathologies such as Aβ plaque accumulation in the brain, as well as indirect outputs such as apoptotic driven neuronal cell death in the brain. Notably, epigenetic alterations in Tip60/HDAC balance precede both Aβ plaque formation and enhanced neuronal apoptosis in the Aβ induced neurodegenerative fly brain. To test whether restoring Tip60/HDAC balance rescues functional deterioration in the fly, we carried out locomotion and survival assays, and demonstrated that both of these processes were defective in the Aβ fly line and were effectively rescued by increasing Tip60 in the nervous system. Our findings support a novel neuroprotective role for Tip60 in AD neurodegenerative pathology solely induced by Aβ42 expression.

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Nanosymposium

354. Amyloid-Beta: Novel Insights Into Function, Toxicity, and Animal Models

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

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The BrightFocus Foundation A2015535S (FML)

Title: Developing mouse models to study late-onset Alzheimer's disease

Authors: *D. BAGLIETTO-VARGAS[1], L. CAI[1], M. T. NGUYEN[1], K. D. HUYNH[1], A. C. MARTINI[1], L. TRUJILLO-ESTRADA[1], C. A. SOTO[2], I. MORENO-GONZALEZ[3], S. VIVEK[1], F. M. LAFERLA[1], &. MODEL-AD CONSORTIUM[1];
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Abstract: Animal models are invaluable tools in our arsenal for studying Alzheimer's disease as they facilitate identification of pathogenic mechanisms and evaluation of therapeutic interventions. The overwhelming majority of AD cases are sporadic, yet virtually all AD genetically-modified rodents incorporate mutant alleles associated with the familial autosomal dominant form of the disease. Our long-term goal is to develop better models to study late onset sporadic AD, which represents a critical new direction for the field. We humanized the Aβ sequence in mice to generate a wild-type human Aβ knock-in model (hAβ-KI mice). We also flanked exon 16 of *App* with loxP sites, allowing for cell-type/temporal control of Aβ production. These mice will be used as a platform to introduce other AD-related human sequences, either via CRISPR technology or via homologous recombination, with the goal of recapitulating critical aspects of AD pathology. The Aβ-KI mice express APP at physiological levels and produce wild-type human Aβ. Age-dependent changes in behavior, gene expression, synaptic plasticity, and histopathology will be presented. Developing a mouse model for late-onset AD poses unique challenges, including that a systematic and long-term approach are required. We completed a critical first step in this process by generating our platform mouse, which will be used as the basis for us to humanize other AD-related genes (TAU, TREM2, APOE, etc.). The UCI group is part of MODEL-AD (https://model-ad.org/), an NIH consortium that seeks to better model late-onset AD and make these resources widely available to the scientific community.

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Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

Location: Room S106

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 355.01

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant NS058487
NIH Grant NS096258

Title: Quantitative separation of tremor and ataxia in essential tremor

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Abstract: The cardinal symptom of essential tremor (ET) is bilateral action tremor, however, ET patients can also experience ataxia. Since ET results from a cerebello-thalamo-cortical dysfunction, it would follow that both ataxia and tremor are potential features, yet quantitative methods to distinguish tremor and ataxia remain elusive. Thus, an important but unresolved question is how much of the disability in ET is a consequence of ataxia and how much is a consequence of tremor. In this study, we test the hypothesis that in ET, dysmetria, which is one manifestation of ataxia, can be separated from tremor. We compared nineteen participants diagnosed with ET who underwent deep brain stimulation (69.8 ± 8.3 yrs., 8 females) to 19 age- and sex-matched healthy controls (HC) (70.1 ± 7.8 yrs., 8 females). Both groups performed postural and fast goal-directed tasks. We quantified tremor of the upper and lower limb during postural tasks using accelerometry. To quantify dysmetria, we used fast goal-directed movements. The reasoning for this methodology was that the endpoint of such movement occurs faster than the tremor frequency and thus minimizes the effect of tremor on the endpoint accuracy. In addition, to ensure that the endpoint accuracy of goal-directed movements was unaffected by tremor, we quantified dysmetria in selected trials manifesting a smooth trajectory to the endpoint. Finally, we manipulated tremor amplitude by performing experiments on ET participants implanted with DBS in the ventral intermediate nucleus of the thalamus (VIM DBS). The following three findings that point to the independence of dysmetria and tremor in ET. First, ET exhibited greater upper and lower limb dysmetria than HC and dysmetria did not correlate with tremor ($R^2 < 0.01$). Second, ET exhibited greater dysmetria than HC even for trials with tremor-free trajectories to the target
($p < 0.01$). Third, activating DBS reduced tremor ($p < 0.01$) but had no effect on dysmetria ($p > 0.2$). Collectively, these results provide novel evidence that dysmetria can be separated from tremor and suggest that ET results in tremor-independent dysmetria.

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Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

Location: Room S106

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 355.02

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: NIH Grant NS58487

Title: Dysmetria exacerbates motor disability in essential tremor patients

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Abstract: Essential Tremor (ET) is a common but heterogeneous disorder. Although all ET patients exhibit action tremor at some body location, a subset of individuals exhibit additional motor and non-motor symptoms. Although there is no strict consensus, the most current classification categorizes ET patients into two groups. The “ET group” is characterized by the presence of bilateral upper-extremity action tremor (postural and/or kinetic) with or without tremor in other locations. The “ET plus group” allows the presence of mild neurological signs (e.g., resting tremor, impaired tandem gait, or impaired memory) however the features defining this group are unclear, as well as how these features relate to tremor, disease severity and motor impairments. Here, we test the hypothesis that ET patients who exhibit dysmetria have increased disability relative to ET patients who exhibit only tremor. Twenty nine ET patients were categorized into a group who exhibited only tremor (ETtremor) and into a group who exhibited dysmetria in addition to tremor (ETdysmetria). We quantified dysmetria as the average endpoint error during wrist and ankle goal-directed movements. We quantified disability with clinical scales of ET disease severity (ratings of tremor, manual dexterity, self-reported disability) and gait and balance impairments. About 50% of the patients we tested (15/29) exhibited dysmetria greater than 29 healthy controls and thus were categorized into the ETdysmetria group. The rest of the patients exhibited only tremor and were categorized into the ETtremor group. These two subtypes of ET were not statistically different in terms of age, disease duration, or cognitive dysfunction (all $p>0.2$). The ETdysmetria group exhibited 36% more disease severity than the ETtremor group when assessed with ET clinical rating scales. Specifically, the ETdysmetria group exhibited impaired manual dexterity ($p<0.01$) and reported greater functional impairement in activities of daily living ($p<0.01$) than the ETtremor group but the clinical rating of tremor was not significantly different between the two groups ($p>0.2$). In addition, relative to the

ETtremor group, the ETdysmetria group also exhibited gait and balance deficits. Specifically, the ETdysmetria group exhibited 31% greater horizontal trunk velocity ($p<0.05$) and 200% greater postural sway ($p<0.001$) than the ETtremor and HC groups. These findings, therefore, provide novel evidence that ET patients who have dysmetria exhibit greater motor disability than ET patients who have only tremor.

Disclosures: B. Yacoubi: None. **A. Casamento Moran:** None. **K.D. Foote:** None. **M.S. Okun:** None. **D.E. Vaillancourt@ufl.edu:** None. **E.A. Christou:** None.

Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

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Presentation Number: 355.03

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: R01 NS 58487 to DEV

Title: Dysmetria contributes to gait and balance impairments in essential tremor patients

Authors: *Y. CHOI, A. CASAMENTO-MORAN, S. DELMAS, S. BRACKSIECK, B. YACOUBI, M. OKUN, D. VAILLANCOURT, E. CHRISTOU;
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Abstract: Essential tremor (ET) is the most prevalent movement disorders in older adults. ET appears to impair gait and balance, as evidenced by their inability to accurately perform tandem gait, slower walking speed, and to perform functional balance tasks. Although, the cardinal sign of ET is bilateral kinetic tremor, growing evidence suggest that ET exhibit impaired endpoint accuracy during goal-directed movements (dysmetria) which is the cardinal symptom of ataxia. However, the contribution of tremor and dysmetria to gait and balance deficits in ET remains unresolved. In this study, we test the hypothesis that dysmetria correlates uniquely to the gait and balance impairments experienced by ET patients. Seventeen ET patients (69.5 ± 8.7 years) and 18 healthy controls (69.5 ± 8.6 years) performed the following tasks: 1) fast goal-directed movements with ankle dorsiflexion (50 trials); 2) quiet standing (3 trials); 3) overground walking for 7 m (3 trials). We quantified dysmetria as the spatial and temporal endpoint error of fast goal-directed ankle movements. We quantified tremor as the power in acceleration from 4-8 Hz in hands and legs during standing with both arms raised forward. We quantified the biomechanics of gait during overground walking and balance during quiet standing using wearable sensors (APDM Inc., Portland, OR). We found that ET patients had significantly higher spatial dysmetria ($p<0.01$), temporal dysmetria ($p<0.05$), hand tremor ($p<0.01$), and leg tremor ($p<0.01$) compared with healthy controls. ET patients exhibited longer time in double support ($p<0.01$) and faster trunk rotational velocity ($p<0.05$) while walking. In addition, ET patients exhibited a longer

sway path length ($p<0.01$) during quiet standing. To examine the contribution of tremor and dysmetria to these impairments, we performed a multiple linear regression model. Tremor predicted the longer time in double support during gait ($R^2=0.39$, $p<0.01$), whereas ankle spatial dysmetria predicted the greater trunk rotational velocity ($R^2=0.34$, $p<0.01$). Leg tremor (part $r=0.46$) and ankle spatial dysmetria (part $r=0.39$) predicted the greater sway path length during quiet standing ($R^2=0.66$, $p<0.01$). These results suggest that in addition to tremor, dysmetria is a significant contributor to gait and balance impairments in ET and should be considered for rehabilitation, which primarily focuses on reducing tremor but not ataxia.

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Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

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Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 355.04

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant NS110100-11

Title: Biomarkers of FXTAS progression in fragile X premutation carriers: Insights from longitudinal neuroimaging

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Abstract: Background: A group of men with the fragile X premutation, along with a group of healthy controls, are being followed longitudinally to examine the trajectory of change in brain structure, brain function, and neuropsychological measures, in an effort to determine factors explaining the early disease process that will occur in some of these men. An inclusion criterion for initial entry to the study was the absence of a diagnosis of FXTAS. Of the men for whom we have collected at least two time points, some have converted to FXTAS between their first and their second visit to the laboratory (which was at minimum 2 years later.)
Methods: Among the carriers seen at follow-up 10 (53-72 years of age, mean = 63.2) began to show evidence of conversion to FXTAS by clinical and neurological exam We compared these individuals to premutation carriers who had not converted to FXTAS between their baseline and second visit. The segmentation of white matter hyperintensities (WMHs) were performed on FLAIR scans using a fully automated tool, lesion prediction algorithm (LPA), implemented in LST (a toolbox of SPM12. The measurements of Middle Cerebellar Peduncles (MCPs) were measured on parasagittal slices and measurements of pons and midbrain areas were assessed on

the mid-sagittal slice, where horizontal lines were drawn through the superior and inferior pontine notches. The segmentations of the corpus callosum (CC) and cerebellar white matter (WM) were performed using multiple-atlas likelihood fusion algorithm implemented in BrainGPS. Functional brain differences were assessed using an fMRI emotion-matching task containing 52 trials each of either emotional faces or shape. Participants responded by button press, to match one of the top images to the target image on bottom. Regions of Interest (ROIs) were defined by selecting 6 mm spheres around the foci of the right and left amygdalae.
Results: Analyses revealed the following in premutation carriers who convert to FXTAS compared to those who do not convert and healthy controls: (a) an initial increase in CC WMHs and atrophy in the cerebellar WM at T1; (b) Significant increase in WMHs from T1 to T2; (c) an initial reduction in MCP width at T1; and (d) a pattern of amygdala activity change from T1 to T2 that mirrors that of FXTAS patients.
Conclusions: Structural and functional neuroimaging measurements hold promise for detecting conversion to FXTAS in premutation carriers who are clinically asymptomatic. These measurements may represent biomarkers with the potential to identify those most at risk for the disorder.

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Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

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Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 355.05

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

Title: Increased cerebrospinal fluid levels of neuroinflammatory markers at an early stage of Alzheimer's disease

Authors: *M. INGELSSON[1], G. BOSTRÖM[1], J. VIRHAMMAR[2], E. FREYHULT[3], D. ALCOLEA[4], H. TUMANI[5], M. OTTO[5], L. KILANDER[1], M. LÖWENMARK[1], V. GIEDRAITIS[1], D. SEHLIN[1], S. SYVÄNEN[1], A. LLEÓ[4], C. A. F. VON ARNIM[5], K. KULTIMA[3];
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Abstract: Background Activated astrocytes and microglia are common features of the Alzheimer’s disease (AD) brain, although the role of these inflammatory changes is largely unknown. For example, it is incompletely understood whether neuroinflammation is beneficial or detrimental to the degenerating brain and whether it appears early or late in the disease process.
Objective To investigate levels of inflammatory markers in cerebrospinal fluid (CSF) from AD

patients at different disease stages. **Methods** Forty-two patients with AD, 21 patients with mild cognitive impairment that later converted to AD (MCI/AD), 22 patients with MCI that remained stable (MCI) and 49 control subjects from three memory disorder units (Uppsala, Sweden; Ulm, Germany; Barcelona, Spain) were included. Five µl of CSF was subjected to measurement of a panel of 92 markers for inflammation with the proximity extension assay technology (PEA, Olink Proteomics, Uppsala, Sweden). Only proteins detected in at least 75% of the samples were included. Linear regression analyses were performed using ANOVA F-tests, comparing mean normalized protein expression units between the diagnostic groups, correcting for age, gender and collection unit. Multiple testing correction was performed using Benjamini-Hochberg's method ($q<0.05$ was considered significant). **Results** Of the 92 proteins tested, 57 (62%) were detected in at least 75% of the samples and therefore included in the study. In the adjusted linear regression analyses, levels of matrix metalloprotease-10 (MMP-10) were 32% higher in AD compared to controls ($q=0.0179$). In the MCI/AD group, 12 of the 57 analyzed proteins were increased ($q<0.05$) compared to the MCI group with MMP-10 levels increased by 38% ($q=0.0111$). None of the markers were found at decreased levels in the AD or MCI/AD groups as compared to the controls and MCI cases, respectively. All results were controlled for confounding factors and multiple comparisons. **Conclusions** Our data indicate that there is a pronounced increase in several markers for inflammation in the CSF at early stages in AD pathophysiology. Of these, MMP-10 levels were increased also at later disease stages. Measurements of inflammatory markers could potentially be utilized for early detection of AD.

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Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

Location: Room S106

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 355.06

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

Support: Life2020 MARBEL
JointLab CrestOptics IIT

Title: Seeing beyond the eye: Neuroinflammatory processes and protein aggregation in the retina of AD patients, possible biomarkers for early diagnosis

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Abstract: Alzheimer's disease is the most common cause of dementia and one of the leading sources of morbidity and mortality in the aging population. The brain AD pathology is characterized by the accumulation of extracellular amyloid-beta peptides, derived from the cleavage of amyloid precursor protein, intracellular deposits of hyper-phosphorylated tau, neurodegeneration, and glial activation. However neuronal and glial modifications occur in the brain long before cognitive deficits, and clinical trials failed, maybe also because of the lack of an early diagnosis. The actual challenge is to define new biomarkers and non-invasive technologies to measure neuropathological changes in vivo at pre-symptomatic stages. Recent evidence on human samples and mouse models indicate the possibility to detect protein aggregates and other hallmarks in the retina, paving the road for non-invasive rapid detection of Alzheimer's disease biomarkers. Here we demonstrate the presence of known and new retinal biomarkers in the human retina of Alzheimer's disease patients. We found the presence of amyloid beta plaques, tau tangles, neurodegeneration and detrimental astrocyte activation in retinal layers. Moreover, retinal microglia showed a disease associated phenotype and astrocytes displayed a typical A1 phenotype. We hypothesize retina as a window through which monitor Alzheimer's disease-related neurodegeneration process.

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Nanosymposium

355. Imaging and Treatment Studies of Essential Tremor and Dementia

Location: Room S106

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 355.07

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: Houston Methodist Nantz Fund

Title: ^{18}F-AV-1451 and ^{11}C-PBR28 inflammation positron emission tomography signal in semantic dementia

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Abstract: Semantic dementia (SD) is typically associated with TDP-43-positive neuropil threads and dystrophic neurites (type C), and only rarely due to a primary tauopathy. However patients

with SD show elevated uptake of the tau PET tracer ^{18}F-AV-1451 in anterior temporal regions. This uptake could be related to non-specific binding, perhaps caused by inflammation, as SD is associated with a propensity for autoimmune disease and increased inflammation in peripheral blood. We studied the association between ^{18}F-AV-1451 uptake and inflammation, measured with the TSPO tracer ^{11}C-PBR28. Six SD patients, all PET amyloid-negative, had ^{11}C-PBR28 and ^{18}F-AV-1451 PET. Fourteen healthy controls underwent ^{11}C-PBR28 PET (n=6) or ^{18}F-AV-1451 PET (n=8). Patients (4/6 women, mean age 69±8.5 years) did not differ significantly in age from the controls (5/14 women, mean age 69±6.7 years). The V_T values for ^{11}C-PBR28 were calculated at the regional level with a Logan plot and a metabolite-corrected arterial input function. The SUV ratio over the cerebellar gray matter for ^{18}F-AV-1451 was calculated for t = 80-100 min. All images were corrected for partial volume effect. A linear regression analysis was performed on V_T and SUVr values in the 64 hemispheric cortical regions of the Hammer's atlas. Compared to controls, patients showed increased V_T and SUVr values in left temporal regions, and in anterior right temporal lobe, as well as in regions of the orbitofrontal cortex adjoining anterior temporal cortex and insular cortex. However, peak uptake of ^{18}F-AV-1451 SUVr localized to the tip of the temporal pole, likely epicenter of neurodegeneration, while the peak of ^{11}C-PBR28 V_T localized to a more posterior, mid-temporal region, likely the margin of spreading damage. Our findings leave the door open for neurobiological processes other than inflammation -including binding to TDP43- to explain the increased ^{18}F-AV-1451 SUVr values in anterior temporal regions in semantic dementia. We also found that neuroinflammation is greatest in the region of disease progression, rather than at where neurodegeneration started, which is a "burned-out" region at the stage when we studied these patients.

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Nanosymposium

356. Mechanisms of Motor Neuron Disease

Location: Room N426

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 356.01

Topic: C.06. Neuromuscular Diseases

Support: GACR 14-10504P
P304/12/GO69
APVV-170642

Title: Mesenchymal stem cells and neural precursors derived from induced pluripotent cells preserve perineuronal nets and stimulate neural plasticity in ALS rats

Authors: *E. M. SYKOVA[1,2], S. FOROSTYAK[3], J. C. KWOK[5], N. ROMANYUK[3], M. REHOROVA[3], R. RAHA-CHOWDHURY[6], P. JENDELOVA[4], J. W. FAWCETT[7,3];

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Abstract: Neurodegenerative diseases (ND) represent a group of diseases with human protein-misfolding and ECM disorders. Astrocytes play a key role in these pathologies as they secrete neurotrophic factors that stimulate neurogenesis, stimulate synaptogenesis and maintain optimal PNNs which are important for neuronal vulnerability and CNS plasticity. Reactive astrocytes are closely associated with disfunction/decrease of extracelluar matrix (ECM) components including perineuronal nets (ALS). We investigated stem cells implantation for their therapeutic potential in neurodegenerative diseases (ND). We found that implantations of human mesenchymal stem cells (MSCs) in animal model of ALS had decreased motoneuronal apoptosis, recovery of motoneuronal PNN and a prolonged lifespan. In our study we show effects of neural precursors derived from human induced pluripotent stem cells (NP-iPS) after multiple intraspinal grafting into asymptomatic and early symptomatic SOD1 G93A transgenic rats. NP-iPS transplantation preserved motoneurons number, slowed disease progression and extended survival of all cell-treated animals. We found that SOD1 G93A rats at the terminal stage have dysregulation of some components of ECM as is versican, has-1, tenascin-R and hapln-1 and spinal chondroitin sulphate proteoglycans (CSPGs). NP-iPS grafting led to normalized host genes expression (*versican, has-1, tenascin-R, ngf, igf-1, bdnf, bax, bcl-2* and *casp-3)* and to a restoration of perineuronal nets around the preserved motoneurones. In the host spinal cord, transplanted cells adopted a glial phenotype or remained as progenitors, many in contact with motoneurons. NP-iPS cells during *in vitro* differentiation toward motoneurons gained their morphological features. Current study implicates dysfunction of ECM-related structures in SOD1 G93A rats and unveil novel mechanisms of NP-iPS action via regulation of host ECM-related genes and proteins. NP-iPS have potent neuroprotective properties and are able to preserve motoneurons and normal structure of the CNS extracellular matrix.
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Nanosymposium

356. Mechanisms of Motor Neuron Disease

Location: Room N426

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 356.02

Topic: C.06. Neuromuscular Diseases

Support: NIH-R21- NS085750-01
Les Turner ALS association

Title: Analysis of molecular pathways involved in health of Alsin deficient corticospinal motor neurons

Authors: *M. GAUTAM[1], L. A. LABOISSONNIERE[4], M. KANDPAL[2], Y. BI[2], J. M. TRIMARCHI[5], R. V. DAVULURI[2], Y. A. GOO[3], P. H. ÖZDINLER[1];
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Abstract: Corticospinal motor neurons (CSMN) play an important role in initiation and modulation of voluntary movement due to their unique ability to collect and integrate signals from different regions of the cerebral cortex and relay that information to the spinal cord targets. Degeneration of CSMN has been a characteristic determinant of hereditary spastic paraplegia (HSP), primary lateral sclerosis (PLS) and amyotrophic lateral sclerosis (ALS). Mutations in various genes are associated with the onset of ALS, leading to motor neuron vulnerability, progressive degeneration, and dysfunction of motor neuron circuitry. Alsin is a member of small GTPases gene family that are involved in cytoskeleton maintenance and vesicle trafficking. Mutations in Alsin gene has been shown to manifest into early ALS onset. The present study was designed to investigate molecular pathways involved in CSMN health. We previously generated and characterized UCHL1-eGFP mice, in which CSMN are genetically labelled with stable and long lasting eGFP expression allowing their specific and precise investigation. The UCHL1-eGFP mice were crossbred with $Alsin^{KO}$ mice to generate $Alsin^{KO}$-UeGFP mice, allowing purification of CSMN that lack alsin function via FACS-mediated approaches. We performed RNA-Seq and proteomics analysis on pure populations of CSMN isolated from $Alsin^{KO}$-UeGFP and $Alsin^{WT}$-UeGFP mice. Our ongoing study reveals key cellular pathways that are affected even at very early stages of the disease. The genes and proteins involved in fatty acid metabolism, immune response, and mitochondrial function were found differentially regulated. Our study reveals the molecular and genetic mechanisms that are involved in the very early stages of neuronal dysfunction in the absence of Alsin.

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Nanosymposium

356. Mechanisms of Motor Neuron Disease

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Presentation Number: 356.03

Topic: C.06. Neuromuscular Diseases

Support: NIH NS091299
MDA 418515
HHMI Gilliam Fellowship for Advanced Study

Title: Glycolysis upregulation is neuroprotective as a compensatory mechanism in ALS

Authors: E. MANZO[1], I. LORENZINI[2], D. BARRAMEDA[1], J. BARROWS[1], T. KOVALIK[3], R. BOWSER[3], R. G. SATTLER[4], ***D. C. ZARNESCU**[1];
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Abstract: Amyotrophic Lateral Sclerosis (ALS), is a fatal neurodegenerative disorder, with TDP-43 inclusions as a major pathological hallmark. Using a *Drosophila* model of TDP-43 proteinopathy we found significant alterations in glucose metabolism including increased pyruvate, suggesting that modulating glycolysis may be neuroprotective. Indeed, a high glucose diet improves locomotor and lifespan defects caused by TDP-43 proteinopathy in motor neurons or glia, but not muscle, suggesting that metabolic dysregulation occurs in the nervous system. Using a genetically encoded glucose sensor we find that motor neurons with TDP-43 proteinopathy have an increased capacity to uptake glucose. Supporting this observation, overexpressing human glucose transporter GLUT-3 in motor neurons mitigates TDP-43 dependent defects in synaptic vesicle recycling and improves locomotion. Furthermore, *PFK* mRNA, a key indicator of glycolysis, is upregulated in flies and patient derived iPSC motor neurons or spinal cords with TDP-43 pathology. Surprisingly, *PFK* overexpression rescues TDP-43 induced locomotor deficits. These findings from multiple ALS models show that mechanistically, glycolysis is upregulated in degenerating motor neurons as a compensatory mechanism and suggest that increased glucose availability is protective.

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Nanosymposium

356. Mechanisms of Motor Neuron Disease

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Topic: C.06. Neuromuscular Diseases

Support: SFI Grant 17/COEN/3474

Title: A systems-level approach to investigate disease-associated metabolic dysfunction in ALS

Authors: ***N. M. CONNOLLY**[1,2], O. WATTERS[1], I. LLORENTE-FOLCH[1], I. FERNANDEZ-PEREZ[1], M. SALVUCCI[1,2], A. MATVEEVA[1,2], D. BANO[3], J. H. PREHN[1,2];

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Abstract: Defects in bioenergetics and carbon metabolism are implicated in multiple neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). Numerous models exist for each disease, however, with varied phenotypes involving complex and disparate signalling processes and converging metabolic pathways. A systems approach is therefore required to fully understand disease-associated metabolic dysfunction during neurodegeneration, and identify appropriate strategies to correct deficiencies in bioenergetics, metabolism, and redox homeostasis. We here present an innovative systems-level approach to analyse disease-model alterations, combining bioenergetic measurements, unbiased molecular profiling, and network-enriched systems analyses. Taking familial ALS as a classical neurodegenerative disease, we investigated three animals models of ALS ($FUS^{(1-359)}$, $TDP43^{A315T}$, $SOD\text{-}1^{G93A}$; both sexes) at pre-symptomatic and symptomatic timepoints. We performed Seahorse bioenergetics measurements on fresh cortical tissue from mutant and wildtype littermates, and mass spectrometry proteomic profiling and RNA-sequencing of cortical and spinal cord tissue from selected animals. We identified various differences in extracellular acidification and oxygen consumption in tissue from pre-symptomatic animals compared to wildtype controls. These differences were altered or absent in tissue from symptomatic animals, suggesting bioenergetic dysfunction specific to pre-symptomatic tissue. These data will be used as input to a computational model of carbon metabolism, to hypothesise putative mechanisms explaining metabolic dysregulation. This systems-level approach is also applicable to other neurodegenerative disorders.

Disclosures: **N.M. Connolly:** None. **O. Watters:** None. **I. Llorente-Folch:** None. **I. Fernandez-Perez:** None. **M. Salvucci:** None. **A. Matveeva:** None. **D. Bano:** None. **J.H. Prehn:** None.

Nanosymposium

356. Mechanisms of Motor Neuron Disease

Location: Room N426

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 356.05

Topic: C.06. Neuromuscular Diseases

Support: VA I01BX004044 (NL)
VA I01BX003755 (BK)
NIH R01NS064131 (BK)

Title: Genome wide analysis reveals heparin sulfate epimerase modulates TDP-43 proteinopathy

Authors: N. LIACKHO[1], A. SAXTON[2], ***B. C. KRAEMER**[1];
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Abstract: Pathological phosphorylated TDP-43 protein (pTDP) deposition drives neurodegeneration in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP). However, the cellular and genetic mechanisms at work in pathological TDP-43 toxicity are not fully elucidated. To identify genetic modifiers of TDP-43 neurotoxicity, we utilized a *Caenorhabditis elegans* model of TDP-43 proteinopathy expressing human mutant TDP-43 pan-neuronally (TDP-43 tg). In TDP-43 tg *C. elegans*, we conducted a genome-wide RNAi screen covering 16,767 *C. elegans* genes for loss of function genetic suppressors of TDP-43-driven motor dysfunction. We identified 46 candidate genes that when knocked down partially ameliorate TDP-43 related phenotypes; 24 of these candidate genes have conserved homologs in the human genome. To rigorously validate the RNAi findings, we crossed the TDP-43 transgene into the background of homozygous strong genetic loss of function mutations. We have confirmed 9 of the 24 candidate genes significantly modulate TDP-43 transgenic phenotypes. Among the validated genes we focused on, one of the most consistent genetic modifier genes protecting against pTDP accumulation and motor deficits was the heparin sulfate-modifying enzyme *hse-5*, the *C. elegans* homolog of glucuronic acid epimerase (*GLCE*). We found that knockdown of human *GLCE* in cultured human cells protects against oxidative stress induced pTDP accumulation. Furthermore, expression of glucuronic acid epimerase is significantly decreased in the brains of FTLD-TDP cases relative to normal controls, demonstrating the potential disease relevance of the candidate genes identified. Taken together these findings nominate glucuronic acid epimerase as a novel candidate therapeutic target for TDP-43 proteinopathies including ALS and FTLD-TDP.

Disclosures: B.C. Kraemer: None. **N. Liackho:** None. **A. Saxton:** None.

Nanosymposium

356. Mechanisms of Motor Neuron Disease

Location: Room N426

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 356.06

Topic: C.06. Neuromuscular Diseases

Title: Delayed transgene expression in a mouse model of ALS and FTLD-TDP demonstrates robust disease phenotype

Authors: *G. CHAN, A. VAN HUMMEL, J. J. VAN DER HOVEN, L. M. ITTNER, Y. D. KE; Fac. of Med. and Hlth. Sci., Macquarie Univ., Sydney, Australia

Abstract: In amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP), the transactive response DNA binding protein 43 (TDP-43)

undergoes several hallmark changes including cytoplasmic mislocalization, ubiquitination, and aggregation. Furthermore, pathological mutations in human TDP-43 are known to cause ALS and FTLD-TDP, and the missense TDP-43-A315T mutation in particular has been shown to cause familial ALS. Our group has previously demonstrated that constitutive expression of TDP-43-A315T in mice (iTDP-43^{A315T}) leads to a complex disease phenotype recapitulating key aspects of ALS/FTLD-TDP.
Here, due to limitations of constitutive transgene expression, we present a further analysis of iTDP-43^{A315T} mice, where transgene expression was suppressed until weaning to allow brain maturation and better model ALS/FTLD-TDP. Transgenic iTDP-43^{A315T} mice (n=13) were compared to pooled littermate controls (n=14) across a range of functional and histological analyses from 6 to 11 months of age. Despite delayed TDP-43-A315T expression, mice nevertheless presented with significant deficits. Muscle atrophy led to weakness in the grip strength and hanging wire challenges, and a loss of coordination in the pole test and on gait analysis. Upon histological examination, TDP-43 showed cytoplasmic mislocalization in neurons and pathological ubiquitination, accompanied by pronounced neurodegeneration in both the hippocampus and cortex. Curiously, these deficits occurred independent of glial activation. Together, these results demonstrate that iTDP-43^{A315T} mice function as a robust model of human disease, with progressive and severe deficits.

Disclosures: G. Chan: None. **A. Van Hummel:** None. **J.J. Van Der Hoven:** None. **L.M. Ittner:** None. **Y.D. Ke:** None.

Nanosymposium

356. Mechanisms of Motor Neuron Disease

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Presentation Number: 356.07

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant AG056678

Title: Resolving the intersection among spinal motor neuron aging and amyotrophic lateral sclerosis in the SOD1G93A mouse model using single nuclei RNA-seq

Authors: *R. HO, P. MATHKAR, D. OHEB, R. ELDER, M. J. WORKMAN, C. N. SVENDSEN;
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Abstract: Amyotrophic lateral sclerosis (ALS) is a late onset, fatal neurodegenerative disorder characterized by the death of motor neurons, leading to skeletal muscle atrophy and ultimately respiratory failure. There are approximately 6,000 new diagnoses of ALS in the United States every year, and patient life expectancy is typically three to five years after disease onset. While

90 percent of ALS cases are sporadic and 10 percent are familial, 20 percent of familial cases are caused by mutations in the superoxide dismutase 1 (SOD1) gene. Understanding the mechanisms at single cell resolution by which SOD1 mutations cause pathogenesis could provide insights into generalizable disease mechanisms in other cases of ALS and thereby guide the development of therapeutic targets. This study aims to quantify changes in RNA expression among SOD1-G93A and wild type mouse spinal cords and mouse induced pluripotent stem cell (iPSC)-derived motor neuron cultures using single nuclei RNA-sequencing. Single cell transcriptomic profiling of central nervous system tissue by cellular dissociation is challenging due to the heterogeneous populations of specialized cell types and complex architectures of cellular processes. Instead, transcriptomic profiling of fractionated, compartmentalized cellular units such as nuclei can effectively capture cellular physiology through RNA expression. Spinal cords were collected from SOD1-G93A and wild type mice at 100, 150, and 200 days post-natal and subjected to single nuclei RNA-sequencing to identify genes that are upregulated or downregulated in ALS conditions throughout the onset and end stage of disease. Additionally, spinal cords were collected from wild type mice at ages 400, 600, and 800 days post-natal and profiled in order to understand the late onset nature of ALS by identifying the intersection of aging pathways disrupted in the ALS condition. Furthermore, we have reprogrammed fibroblasts from SOD1-G93A and wild type mice to generate iPSC lines to be differentiated *in vitro* to spinal tissue and profiled similarly. Comparison of single nuclei gene expression between the *in vitro* and *in vivo* systems aims to assess the fidelity of stem cell models of ALS and ultimately improve human iPSC models of ALS, as well as other late onset diseases.

Disclosures: R. Ho: None. **P. Mathkar:** None. **D. Oheb:** None. **R. Elder:** None. **M.J. Workman:** None. **C.N. Svendsen:** None.

Nanosymposium

356. Mechanisms of Motor Neuron Disease

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Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 356.08

Topic: C.06. Neuromuscular Diseases

Support: Muscular Dystrophy Association - MDA
California Institute for Regenerative Medicine - CIRM

Title: VAPB mutation associated with ALS leads to increase in mRNA translation and motor neuron demise in patient derived cells

Authors: *H. C. MIRANDA[1], R. HERAI[2], M. MITNE-NETO[3], G. WONG[4], J. MORESCO[6], J. OKUBO[4], J. R. YATES, III[7], M. ZATZ[8], A. R. MUOTRI[5];
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Abstract: ALS is a complex disorder, involving multiple cellular and genetic. The ALS field acknowledges that a substantial number of drugs found to alleviate symptoms in ALS animal models failed in clinical trials. One reason for this lack of success is the use, mainly of pathways identified in a single model - SOD1 mice carrying a high transgene copy number. Consequently, the use of patient derived cells holds great promise for the discovery of new therapeutic targets. We pioneered in this field by describing the first ALS *in vitro* model with a clear molecular phenotype, based on VAMP associated protein B (VAPB) mutant (VAPB-P56S) ALS patient-derived induced pluripotent stem cells (iPSCs). VAPB is a protein anchored to the membrane of the ER and previous studies have implicated ER stress and more recently autophagic defects as mechanisms of VAPB toxicity. A reduction in VAPB levels was found not only in our iPSC derived motor neurons from VAPB-P56S patient but also in sporadic ALS patients and transgenic SOD1 mice. Recently, we have identified binding partners of VAPB significantly associated to the mTOR pathway. Additionally, we have also identified mitochondria dysregulation and a subsequent alteration in electrophysiological activity, analyzed by multi electrode array (MEA). It is known that mTOR controls mRNA translation and mitochondrial function through eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) translation regulation. However, the effect of the mutation in VAPB to mRNA translation, is yet to be understood. Our group revealed increased levels of phosphorylated 4EBP1 (p4EBP1) in VAPB-P56S iPSCs-derived motor neurons and a concomitant increase in mRNA translation. Therefore, our results implicate mitochondria dysregulation and mRNA translation in VAPB-P56S patients compared to their familial controls, and pinpoint altered mTOR signaling pathway function as a pathological turning point resulting in altered electrophysiological activity. To our knowledge, this is the first time mRNA translation is reported to be increased in a neurological disease. The results presented here, uncover new therapeutic opportunities for VAPB-P56S ALS, with possible implications to sporadic ALS as well.

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Nanosymposium

357. Pain Imaging and Perception

Location: Room S403

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 357.01

Topic: D.03. Somatosensation – Pain

Support: Fonds de Recherche du Québec en Santé

Title: Pain hypersensitivity and enhanced olfactory performance is associated with brain plasticity in the blind mouse

Authors: *S. TOUJ[1], R. TOKUNAGA[1], S. AL AIN[1], D. R. GALLINO[2], M. CHAKRAVARTY[2], G. BRONCHTI[1], M. PICHE[1];
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Abstract: Vision is crucial for interacting with the environment, including behavioral adaptation to protect the body's integrity. Visual deprivation results in brain plasticity, including a rewiring of cortico-cortical connections and volumetric changes in cortical and subcortical regions. This plasticity is closely related to behavioral changes, including enhanced tactile and auditory performance. However, little is known about olfaction and pain perception in the blind. Conflicting results were reported on olfaction, but some studies showed enhancement of olfactory performance in blind individuals. As for pain perception, a few studies indicate that congenitally blind individuals show thermal hyperalgesia. The aim of the present study was to examine brain plasticity and changes in pain perception and olfaction in a mouse model of congenital blindness to determine if functional changes occurring in the blind are associated with changes in the morphology of brain regions related to pain and olfaction. Brain morphology was compared between blind and sighted mice using structural MRI and deformation-based morphometry. The formalin test, von Frey test, acetone drop test, and tail-flick test were conducted to assess sensitivity to painful stimuli in different modalities, while olfactory performance was assessed using the olfactory sensitivity test and the buried food test. The MRI experiment indicates that the volume of several olfactory structures (olfactory bulbs, anterior olfactory nucleus, accessory olfactory bulb, piriform cortex, orbitofrontal cortex) and the amygdala are increased in blind compared with sighted mice. In addition, behavioral assessment indicates that blind mice show pain hypersensitivity to chemical, mechanical, cold and heat stimuli, compared with sighted mice. Furthermore, pain-related activity in the amygdala was increased in blind compared with sighted mice, as shown by increased c-Fos immunoreactivity in the amygdala ($p < 0.001$), including its central nucleus specifically ($p < 0.001$). Besides, blind mice showed better performance than sighted mice in both olfactory tests. These results indicate that blind mice exhibit hypersensitivity to acute pain that may be associated to the structural and functional plasticity evidenced in the amygdala. Furthermore, the enlargement of several olfactory areas observed in blind mice may contribute to enhanced olfactory performance.

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Nanosymposium

357. Pain Imaging and Perception

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Presentation Number: 357.02

Topic: D.03. Somatosensation – Pain

Support: BBSRC Grant BB/R00823X/1

Title: Pain related activity in the somatosensory cortex and the medial prefrontal cortex of adult awake male rats is altered by early life pain experience

Authors: P. CHANG, R. ALIWALAS, S. BEGGS, *M. FITZGERALD;
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Abstract: The importance of pain in young mammals goes beyond the immediate need to prevent suffering; there is increasing evidence that pain and injury in early life causes lasting changes to developing somatosensory and pain systems. Previous studies have shown that rat pups exposed to plantar incision injury at a critical stage of development display enhanced pain behaviour and altered brainstem descending pain controls, when they are adults. Here we investigated whether this 'priming' by early life tissue injury alters the functional development of cortical pain networks. Using telemetric recording in adult awake male rats, we recorded local field potentials and analysed oscillatory activity in the somatosensory cortex (S1) and medial prefrontal cortex, (mPFC). We first analysed background activity before and after adult hindpaw skin incision (2 hours, 4 & 10 days) in 'primed' rats (that had experienced hind-paw incision injury at postnatal day (P)3) and controls. Following adult skin incision in controls, oscillatory energy in mFPC increased in the gamma range accompanied by longer periods of wakefulness, for up to 10 days post-incision (n=3). Surprisingly, these changes did not occur in 'primed' rats where mPFC activity (n=4) was not different from naïve, uninjured rats (n=4). Next we analysed event related cortical activity during von Frey hair (vFh) mechanical stimulation of the adult incision area. As previously reported, primed rats displayed significantly prolonged behavioural mechanical hyperalgesia following hindpaw skin incision compared to controls (primed, 37.57 ± 3.74g; control 51.23 ±1.03g, vFh threshold 4 days post incision). This was associated with prolonged changes in brain activity, comprising reduced power in the low frequency range (1-20 Hz) especially in mPFC (n=5). Analysis of phase amplitude coupling indicated changes in theta and gamma coupling that were more prolonged in primed animals than in controls. Our results reveal how exposure to painful sensory experience in early life significantly affects adult pain-related brain networks.

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Nanosymposium

357. Pain Imaging and Perception

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Presentation Number: 357.03

Topic: D.03. Somatosensation – Pain

Support: NIDA Grant 5K08DA037525

Title: The structure and function of the nucleus accumbens in subacute and chronic low back pain

Authors: *P. Y. GEHA[1], ***M. M. MAKARY**[2], P. POLOSECKI[3], I. E. DE ARAUJO[4], D. S. BARRON[5], R. T. CONSTABLE[6], G. A. CECCHI[8], D. M. SMALL[7];
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Abstract: Introduction:
Chronic pain is a huge burden to individuals and society. Despite recent literature showing a role for the limbic system in the pathophysiology of chronic pain, brain biomarkers associated with chronic back pain (CBP) and with the transition from sub-acute to chronic back pain remain understudied. In this study we examined the volume of sub-cortical limbic structures in patients suffering from sub-acute back pain (SBP) and patients suffering from CBP. We also followed a sub-group of the SBP patients after one year of initial testing to identify patients who persist in having pain (SBPp) and patients who recover (SBPr).

Methods
The study recruited 40 SBP patients, 29 CBP patients, and 30 healthy controls (HC). All SBP patients reported pain of at least 20/100 on visual analogue scale for the previous 6 to 16 weeks with no back pain or pain at other locations in the 12 months prior to the onset of the current episode. CBP patients reported pain of at least 30/100 on a VAS for at least one year. All participants underwent a structural (MPRAGE) and a functional scan at rest at entry into the study. The SBP patients and HC were followed at one year. 35 SBP patients returned for a follow-up behavioral testing at one year 26 of whom underwent another session of structural and functional imaging at one year. 14 HC underwent another session of structural and functional imaging at one year. Structural brain data and preprocessing of the resting fMRI time series were analyzed with the FSL software library. We examined subcortical volumes using FIRST part of FSL and seed connectivity (*fc*) and power spectral density (PSD) of brain activity using custom Matlab routines.

Results
Structural analysis of sub-cortical volumes showed a gradual decrease in left nucleus accumbens (LNAc) volume from HC to SBP and CBP patients ($p < 0.05$). SBPp patients whose pain persisted at one year showed also a significant decrease in the LNAc at baseline and at one-year follow-up compared to HC ($p < 0.05$). Recovered SBPr patients LNAc volume was not different from HC. LNAc volume did not show a significant change over one year. Next, *fc* of putative NAc shell and core. Notably, the difference in *fc* between putative shell and core showed an increase in superior parietal lobule of SBPr patients at baseline and increase in the rostral cingulate (rACC) of SBPp patients at one-year follow-up when compared to HC. The *fc* difference in rACC was linearly correlated to low back pain intensity at one year ($r = 0.60$, $p <$

0.01). Finally, PSD analysis showed loss of power in slow frequency band (0.01-0.027 Hz) in CBP patients and in SBPp patients within the NAc.

Conclusion

The NAc is a potential biomarker of pain and the risk of pain chronification.

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Nanosymposium

357. Pain Imaging and Perception

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Presentation Number: 357.04

Topic: D.03. Somatosensation – Pain

Support: NIH Grant 1P50DA044121-01A1

Title: Whole-brain functional network disruption in chronic pain with disc herniation

Authors: S. HUANG[1], K. WAKAIZUMI[2], B. WU[1], B. SHEN[1], B. WU[1], L. FAN[1], M. N. BALIKI[3], G. ZHAN[1], A. V. APKARIAN[2], ***L. HUANG**[2];
[1]The Second Affiliated Hosp. and Yuying Children's Hosp. of Wenzhou Med. Univ., Wenzhou, China; [2]Northwestern Univ., Chicago, IL; [3]Shirley Ryan AbilityLab, Chicago, IL

Abstract: Brain functional network properties are globally disrupted in multiple chronic pain conditions. Back pain with lumbar disc herniation is highly prevalent and a major route for progression to chronic back pain. However, brain functional network properties remain unknown in such patients. Here, we examined resting-state fMRI-based functional connectivity networks in chronic back pain patients with clear evidence for lumbar disc herniation (LDH-CP, n = 146), in comparison to healthy control counterparts (HC, n = 165) in China. The data was equally subdivided into Discovery and Validation subgroups (n = 68 LDH-CP and n = 68 HC, for each subgroup) according to demographic and clinical behavior measures and contrasted to an off-site dataset (n = 272, NITRC 1000).

We examined degree, clustering coefficient and local efficiency, the topological properties characterizing network hubness, segregation and integration respectively. We found that global disruption indices derived from those three properties (K_D_D, K_D_CC and K_D_E) were significantly lower in LDH-CPs compared to HCs. This finding was consistent across all predefined link densities (2-10%), in both discovery and validation groups. On the other hand, global mean clustering coefficient and betweenness centrality were decreased in the discovery group while showed similar trend in the validation group. Finally, when associating these network disruptions with principle components derived from clinical behavior measures, we discovered a negative correlation between graph disruption indices and pain intensity, which was

limited to males with high education.
These results suggested that there's a whole-brain functional network topology disruption in LDH chronic pain patients, the extent of the disruption is associated with pain intensity and that such association can be affected by demographic background. These results deviate somewhat from recent studies on other musculoskeletal chronic pain conditions, yet we cannot determine whether the differences are related to distinct pain clinical syndromes or also to cultural differences between patients studied in different countries.
Keywords: Lumbar Disc Herniation, resting-state fMRI, chronic pain, brain network disruption

Disclosures: S. Huang: None. **K. Wakaizumi:** None. **B. Wu:** None. **B. Shen:** None. **B. Wu:** None. **L. Fan:** None. **M.N. Baliki:** None. **G. Zhan:** None. **A.V. Apkarian:** None. **L. Huang:** None.

Nanosymposium

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Topic: D.03. Somatosensation – Pain

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Title: Cortical thickness-guided prediction of long-term pain relief following gamma knife radiosurgery for trigeminal neuralgia

Authors: *P. S.-P. HUNG[1], J. Y. ZHANG[2], A. NOORANI[1], M. HODAIE[1];
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Abstract: Introduction: Trigeminal neuralgia (TN) is a severe unilateral chronic facial pain disorder with well-documented nerve-level white matter and brain-level gray matter changes. Around 20% of TN patients fail to achieve long-term relief of pain following surgical interventions for TN. Accurate pre-treatment prognostication tools for long-term response to TN surgeries is therefore helpful for clinical decision making. Recent work from our group has shown that machine learning (ML) models built from nerve-level features are reasonably effective (71.0% accurate) at predicting long-term responders from non-responders to TN surgeries; however, it is possible that pre-treatment brain-level features may also serve as predictors of long-term pain relief. We aimed to create a ML model able to prognosticate long-term response to radiosurgery for TN from pre-treatment cortical thickness measurements with superior prognostication abilities than prior models. Methods: A total of 51 TN patients (18 M, 33 F, 62 ± 13.6 SD years old) who underwent radiosurgery as their first surgical treatment for TN with high-resolution pre-treatment, 3-Tesla T1 weighted anatomical magnetic resonance

imaging (MRI) were included in this study. Freesurfer 6.0 was used to measure cortical thickness from the 68 brain regions defined in the Desikan-Killiany atlas. Based on 75% reduction from baseline pain intensity as a threshold at 1-year post-treatment time-point, patients were then subdivided into non-responder and long-term responder subgroups. Using scikit-learn, a support vector machine (SVM) model was then built using cortical thickness measurements, patient age, sex, TN pain laterality as input features to predict long-term response. Results: Using pre-treatment brain cortical thickness data, we produced a SVM model that was cross-validated to be 76.5% accurate at predicting long-term response to surgical interventions for TN. Furthermore, based on cross-validated SVM weights, the top-5 predictive features in our model were cortical thickness measures from brain regions within default mode, salience, and limbic functional networks. Conclusion: We demonstrated that a ML model built on pre-treatment cortical thickness data is predictive of long-term response to radiosurgery for TN. The cross-validated performance of our current, brain-based model surpassed those of prior models. Since our model is based on readily available T1 MRI data, it holds strong clinical translational potential. To realize this potential, future studies should assess our model's broader, multi-site generalizability.

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Nanosymposium

357. Pain Imaging and Perception

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Topic: D.03. Somatosensation – Pain

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R61 AT009306

Title: Striatal hypofunction as a neural correlate of mood alterations in chronic pain patients

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Abstract: Chronic pain and mood disorders share common neuroanatomical substrates involving disruption of the reward system. Additionally, increase in negative affect (NA) and decrease in positive affect (PA) are well-known factors complicating the clinical presentation of chronic pain patients. Nonetheless, our understanding of the mechanisms underlying the interaction between pain and PA/NA remains limited. Here, we used a validated task probing behavioral and neural responses to monetary rewards and losses in conjunction with functional magnetic resonance imaging (fMRI) to test the hypothesis that striatal dysfunction relates to mood alterations comorbid with chronic pain. Twenty-eight chronic musculoskeletal pain patients (chronic low back pain, CLBP; n=15; fibromyalgia, FM; n=13) and 18 healthy controls (HC) underwent four ~5-minute BOLD fMRI scans, each corresponding to one initial calibration and three experimental runs (TR/TE=2s/30ms, flip angle=90°, voxel size=3.1x3.1x3mm, 37 slices, 142 volumes), fMRI while performing the Monetary Incentive Delay (MID) task. Behavioral and neural responses were compared across groups and correlated against measures of depression (Beck Depression Inventory) and hedonic capacity (Snaith-Hamilton Pleasure Scale). Compared to controls, patients demonstrated higher anhedonia and depression scores, and a dampening of striatal activation and incentive-related behavioral facilitation (reduction in reaction times) during reward and loss trials of the MID task (ps<0.05). A HC>CLBP>FM gradient was observed for all principal outcomes evaluated, whereby the dampening of the behavioral and striatal response to reward and loss cues, as well as the levels of negative affect and anhedonia were all greatest in FM patients, followed by CLBP patients. Across all participants, lower activation of the right striatum during reward trials was significantly correlated with lower incentive-related behavioral facilitation and higher anhedonia scores (ps<0.05). Finally, among patients, lower bilateral striatal activation during loss trials were correlated with higher depression scores (ps<0.05). Our data suggests that striatal hypofunction is a neural correlate of mood alterations in chronic pain patients.

Disclosures: M. Kim: None. **I.A. Mawla:** None. **D.S. Albrecht:** None. **R. Admon:** None. **A. Torrado-Carvajal:** None. **C. Bergan:** None. **E. Protsenko:** None. **P. Kumar:** None. **R. Edwards:** None. **A. Saha:** None. **V. Napadow:** None. **D.A. Pizzagalli:** None. **M.L. Loggia:** None.

Nanosymposium

357. Pain Imaging and Perception

Location: Room S403

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 357.07

Topic: D.03. Somatosensation – Pain

Support: Queen Elizabeth II/Purdue Pharma Graduate Scholarship in Science and Technology

Title: Lesional trigeminal neuralgia: A new subtype of trigeminal neuralgia attributed to a single brainstem lesion

Authors: *S. TOHYAMA[1,2], P. S. P. HUNG[1,2], J. C. CHENG[3], J. Y. ZHANG[2], M. HODAIE[1,2]; [1]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada; [2]Krembil Res. Inst., Toronto, ON, Canada; [3]Stony Brook Univ. Sch. of Med., Stony Brook, NY

Abstract: Background & Aims: Trigeminal neuralgia (TN) is one of the most severe types of chronic pain, characterized by a sudden jolt of electric shock-like unilateral facial pain. Although not essential to TN pathophysiology, a well-established etiological factor is neurovascular compression of the trigeminal nerve. Here we identify a large subgroup of patients that conform to the diagnosis of classic TN, but with the unique MRI finding of a single, isolated, plaque-like lesion in the brainstem. Importantly, these patients lack any features that would suggest the diagnosis of TN secondary to multiple sclerosis (MS-TN). We aim to propose this new subtype of TN, which we name lesional trigeminal neuralgia (LTN), by combining clinical and advanced neuroimaging analyses. **Methods**: 481 patients with classic TN that underwent surgical treatment were retrospectively reviewed for the presence of a single brainstem lesion. 25 LTN patients were identified (15 men and 10 women, mean age ± SD: 70.4 ± 10.9 years), 20 of which had clinical follow-up to determine long-term surgical response. Lesion mapping was performed to determine lesion sites and its association with pain. Diffusion-weighted imaging scans were acquired on a subset of 12 LTN patients. Diffusion tensor imaging was used to examine the white matter abnormalities of the lesions and tractography performed to pinpoint the trigeminal brainstem tracts. Fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity were extracted from the (1) LTN lesions, (2) MS-TN brainstem plaques, (3) contralateral, unaffected side, (4) and matched healthy controls. **Results**: 19/20 of LTN patients were refractory to surgical management (mean number of surgeries ± SD: 3.95 ± 2.33, range: 1-9). The lesions were unanimously located along the brainstem trigeminal fibers on the painful side, where the greatest lesion overlap across patients was at the spinal trigeminal nucleus. Diffusion tensor imaging revealed significant microstructural differences between LTN lesions and MS-TN brainstem plaques using a tract-restricted approach ($P < 0.05$). **Conclusions**: A clear definition and knowledge of this syndrome may greatly advance the clinical decision-making of these patients, as they are refractory to all forms of current treatment. This study also highlights the fundamental role of the CNS in the maintenance of chronic pain and how advanced neuroimaging analyses can reveal potential pathophysiological mechanisms and identify key features that highlight non-response to treatment for pain.

Disclosures: S. Tohyama: None. **P.S.P. Hung:** None. **J.C. Cheng:** None. **J.Y. Zhang:** None. **M. Hodaie:** None.

Nanosymposium

357. Pain Imaging and Perception

Location: Room S403

Time: Monday, October 21, 2019, 1:00 PM - 3:00 PM

Presentation Number: 357.08

Topic: D.03. Somatosensation – Pain

Support: CIHR
Mayday Fund

Title: Does abnormal alpha, beta, and gamma band power represent a general marker of neuropathic pain?

Authors: *K. D. DAVIS[1,2], L. B. KISLER[1], J. A. KIM[1,2], K. S. HEMINGTON[1,2], A. ROGACHOV[1,2], R. L. BOSMA[1], N. R. OSBORNE[1,2], R. D. INMAN[1,2];
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Abstract: Objective and Rationale: We have reported that patients with multiple sclerosis (MS)-related neuropathic pain (NP) exhibit slowing of the MEG alpha peak frequency and reduced beta-band power in the dynamic pain connectome (DPC)[1,2], which was related to pain severity and pain interference. Here our aim was to examine whether these findings are specific to MS or represent general aberrant temporal dynamics in NP. Gamma band activity has also been associated with pain perception[3,4]. Thus, here we measured multiband resting state MEG spectral density in patients with chronic back pain due to ankylosing spondylitis (AS), a spondyloarthritis with mixed neuropathic and inflammatory pains.
Methods: Resting state MEG data were acquired from 38 AS patients (26 male, 12 female) and age/sex matched healthy controls (HC). We assessed NP using the painDETECT to divide patients into non-NP (NNP) (scores<13) and mixed-NP (NP) (scores≥13) groups. Pain, pain interference, and disease activity were assessed using the Brief Pain Inventory (BPI), and Bath AS Disease Activity Index (BASDAI). We performed beamforming and regional spectral power analysis (theta, alpha, beta, low gamma frequencies (4-60Hz)) in the DPC, including nodes of the ascending nociceptive pathway (ANP), default mode (DMN), and salience networks (SN).
Results: Compared to HCs, AS patients had increased theta (4, 6Hz) power in the DMN (medial prefrontal cortex, mPFC) and decreased low gamma power in the DMN (mPFC), SN (right anterior insula, (aINS), mid-cingulate cortex, dorsolateral (PFC, DLPFC)), and ANP (S1, S2, posterior insula, pINS). Of note, no group differences were found for the beta band frequency. These differences were driven by the NP group. Further, compared to both NNP and HC, NP patients had increased alpha power in the DMN (mPFC), SN (temporal-parietal junction, aINS, DLPFC) and ANP (S1, S2, pINS). In the alpha range, NNP showed a significant negative correlation between the BASDAI score and power within the ANP (thalamus, TH, S2, pINS), while the NP showed a significant positive correlation between trait pain and alpha power in the DMN (mPFC), SN (aINS), and ANP (TH, S1, pINS).
Conclusion: These data suggest that our previous findings[1] of temporal abnormalities in the DPC in MS patients are a general marker of neuropathic pain.

References:
1. Kim JA., et al, 2019. *Pain 160*, 187-197.
2 . Kucyi A, Davis KD 2015. *Trends Neurosci 38*, 86-95.
3. Nickel MM et al. 2017. *Neuroimage 148*, 141-147.
4. Ploner M, May ES 2018. *Pain 159*, 206-211.

Disclosures: K.D. Davis: None. **L.B. Kisler:** None. **J.A. Kim:** None. **K.S. Hemington:** None. **A. Rogachov:** None. **R.L. Bosma:** None. **N.R. Osborne:** None. **R.D. Inman:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.01

Topic: D.04. Somatosensation – Touch

Support: DFG-SFB1089
HFSP

Title: Neuronal coding for a sudden change of stimulation frequency in the barrel cortex of mice

Authors: *A. PARABUCKI, Y. ORAN, M. SOKOLETSKY, Y. A. KATZ, I. LAMPL; Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Rodents perceive their surroundings by iterative active whisking at frequencies ranging from 5 to 25 Hz. The effect of each rate on neural response is typically probed by repetitively stimulating the whiskers at that rate. Many studies showed that repetitive stimulation of the whiskers causes synaptic depression at all stages of sensory processing, from brainstem to cortex. However, the role of synaptic facilitation in sensory processing is barely understood, despite being extensively studied in brain slices. We hypothesized that facilitation may be the mechanism underlying detection of change in somatosensory environment. To test this in vivo we observed the response to a sudden change of stimulation frequency in L2/3, L4 and L5 neurons in S1. We stimulated single whiskers with two alternating frequencies (combinations of 4, 8, 10, 16, 24, 40 Hz, train stimuli) while performing whole-cell or juxta-cellular recordings in both anesthetized and awake head-fixed GAD-ChR2 mice. Given that it is difficult to stimulate whiskers in a precise manner in awake rodents due to whisking, we have unilaterally severed the buccolabialis branch of the facial nerve to eliminate whisking movements. We revealed two functionally distinct groups of S1 neurons with respect to their response to increase in stimulation frequency (high switch). One group of cells responded as expected from short-term synaptic models which predict that due to depletion of synaptic resources, the response to a sudden increase in stimulation frequency will entail even greater depression. However, the second group of neurons, although adapted to the initial train of stimuli, exhibited facilitation

following the high switch. Interestingly, both inhibitory and excitatory neurons (identified optogenetically) were found in these two groups. Voltage clamping the cells showed that the facilitation was not due to temporal summation of inputs or reduced inhibitory drive, but rather due to synaptic facilitation of excitation. These results were further substantiated using 2-photon calcium imaging in awake mice, which revealed that a large fraction of S1 cells exhibited a prominent facilitation in response to the sudden change in stimulation frequency. In summary, our results demonstrate the coexistence of two populations of neurons based on their response to a sudden change in stimulation frequency. Synergistic integration from these two populations may enhance the ability to detect rapid changes in the rate of incoming tactile inputs during exploration or when passively exposed to moving stimuli.

Disclosures: **A. Parabucki:** None. **Y. Oran:** None. **M. Sokoletsky:** None. **Y.A. Katz:** None. **I. Lampl:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.02

Topic: D.04. Somatosensation – Touch

Support: SNSF 31003A_182010
EU-MSCA 798617
Brain Science Foundation 2018

Title: Optical measurement and perturbation of global cortical processing for context-dependent behavior

Authors: *K. TAMURA, V. ESMAEILI, S. CROCHET, C. C. PETERSEN;
Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, Switzerland

Abstract: We can change our behavior by judging contexts, but the neural mechanisms underlying such context-dependent behavior remain unclear. Here, we studied dynamic changes in global cortical circuits between different behavioral contexts. First, we performed optogenetic stimulation mapping of the dorsal cortex in Thy1-ChR2 mice, and localized the tongue/jaw motor area in which optogenetic stimulation evoked jaw-opening movements. Interestingly, stimulation of this area in Thy1-ChR2 mice provoked tongue protrusion movements only in contexts where mice could lick for liquid reward, suggesting important context-dependence of cortical motor maps. Next, we performed wide-field calcium imaging in transgenic mice expressing a red fluorescent calcium indicator during a context discrimination task. In the task, mice licked for reward in response to an auditory ‘go’ cue when a preceding whisker contextual cue predicted the availability of reward, while mice withheld licking after the ‘go’ cue when

there was no contextual cue. In correct trials, the cortical activity after the auditory 'go' cue expanded to tongue/jaw area only when the whisker contextual cue predicted the reward availability. Finally, to address circuit mechanisms that underlie the observed context-dependent changes, we have begun to combine optogenetic manipulations together with wide-field calcium imaging. We find that optogenetic stimulation of one area can also profoundly affect other cortical regions. For example, by stimulating the whisker somatosensory area by single short light pulses, a focal calcium response was remotely evoked in the frontal area of the cortex, consistent with the known anatomical projection from somatosensory to motor cortex. Systematic stimulation of different sites of the cortex evoked focal responses in different sites, which revealed a map of directional connectivity in dorsal cortex. The current results suggest that context can switch the functional and causal states of cortical circuits to produce appropriate behavioral outputs in each context. Mapping directional cortical connectivity in different task contexts will be useful to further reveal how cortical circuits are switched by behavioral demands and learning.

Disclosures: K. Tamura: None. **V. Esmaeili:** None. **S. Crochet:** None. **C.C. Petersen:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.03

Topic: D.04. Somatosensation – Touch

Support: 1R01NS094396

Title: Modulating the amplitude of intracortical microstimulation reveals distinct recruitment mechanisms of local and distant neurons as seen by *in vivo* two-photon microscopy

Authors: T. D. KOZAI[1], J. R. ELES[2];
[1]Bioengineering, [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Over the past 30 years, intracortical microstimulation (ICMS) has been developed to provide phosphene generation in cortical visual prosthetics, and more recently to provide somatosensory feedback in brain-computer interface applications. To control the sensations evoked by ICMS, the stimulation waveform can be modulated across a vast parameter space of pulse width, frequency, shape, duration, temporal patterning, and amplitude. It is thought that increases in amplitude will increase the radius of the suprathreshold electric field, which in turn recruits a larger radius of neurons. As axons within the radius of activation are recruited, antidromic activation of distant cells also occurs, leading to sparse neuronal activation. In the present work, we expand upon this model using two-photon imaging of ICMS in the somatosensory cortex of transgenic mice expressing the calcium sensor GCaMP6s in excitatory

cortical neurons, as well as mice with a virally expressed glutamate sensor (iGluSnFr) in cortical neurons. Using long-duration ICMS trains, we show that fewer cells far from the electrode site (> 60μm) can maintain activation during the ICMS train compared to cell populations close to the electrode. As amplitude is increased, the number of distant cells that maintain activation also increases. With increases in amplitude, the fluorescence of neuronal somas and surrounding neuropil becomes more correlated in the local and distant environments. We also show that, in contrast to previous publications, glutamate release is prominent during ICMS, but that it is largely confined within the local region of the electrode site. These results ultimately support the model of antidromic activation of distant cells during ICMS, and further show that this distant population of cells fatigue more rapidly.

Disclosures: T.D. Kozai: None. **J.R. Eles:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.04

Topic: D.04. Somatosensation – Touch

Support: NIH/NINDS Grant 095251

Title: The perceptual correlate of ICMS frequency varies across somatosensory cortex

Authors: T. CALLIER, ***N. BRANTLY**, S. BENSMAIA;
Univ. of Chicago, Chicago, IL

Abstract: Intracortical microstimulation (ICMS) can be used to convey sensory feedback in brain-controlled bionic hands, thereby conferring to them improved dexterity. ICMS-evoked percepts are shaped by the stimulation parameters, including pulse charge, pulse patterning, and electrode location. That the evoked sensory percept depends on ICMS frequency has been previously established, but only over a narrow range of frequencies. Furthermore, the sensory consequences of changes in frequency have not been systematically probed. Indeed, while animals could discriminate between pulse trains that varied in frequency, their discrimination judgments may have relied on stimulus intensity, given the frequency dependence of sensitivity to ICMS. To fill these gaps, we investigated ICMS frequency discrimination over a wide range (10 to 400 Hz) and gauged whether changes in frequency affect the quality of the evoked percept in addition to its perceived intensity. We trained rhesus macaques to discriminate the frequency of pulse trains delivered to somatosensory cortex. ICMS amplitude varied randomly from stimulus to stimulus so that animals could not rely on differences in perceived intensity to make their judgments. First, we found that animals could reliably discriminate frequency up to approximately 200 Hz when stimulus amplitudes were equal. Second, we found that amplitude

exerted a systematic bias on monkeys' frequency discrimination judgments and that the strength of this bias varied widely across electrodes. Third, we tested a variety of models to account for behavioral performance and conclude that, in some cases, changes in frequency only affect the perceived magnitude of the evoked percept while, in others, they also affect its quality. In the latter case, changes in sensory quality reflect changes in the temporal structure of ICMS-induced activity rather than changes in the strength of the evoked population response. While heterogeneity across electrodes must be taken into consideration, we conclude that ICMS frequency may be leveraged to shape the quality of artificial tactile percepts.

Disclosures: T. Callier: None. **N. Brantly:** None. **S. Bensmaia:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.05

Topic: D.04. Somatosensation – Touch

Support: R01 NS 101325

Title: Is this good silk or cheap silk? High level representations of texture in lateral parietal cortex

Authors: *K. H. LONG[1], S. J. BENSMAIA[2];
[2]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL

Abstract: Our exquisite sensitivity to surface texture spans six orders of magnitudes in spatial scale - from tens of nanometers to tens of millimeters - and allows us to identify objects by touch alone and to apply adequate, but not excessive, force when grasping them. In the peripheral nerves, coarse features are encoded in the spatial pattern of activation of one population of mechanoreceptive afferents, while fine features are encoded in the precise temporal patterns of activation in another. These separate streams of information are integrated to give rise to highly idiosyncratic responses in neurons of somatosensory cortex, yielding a high-dimensional representation of texture. In this study, we assessed how texture signals are further processed in lateral parietal cortex (LPC), a high-level tactile processing area. To this end, we trained a monkey to perform a same-different texture discrimination task and recorded from neurons in LPC, including secondary somatosensory cortex (S2) and the parietal ventral area (PV). We then characterized the texture responses in LPC and compared them to their counterparts in somatosensory cortex.

Disclosures: K.H. Long: None. **S.J. Bensmaia:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

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Presentation Number: 358.06

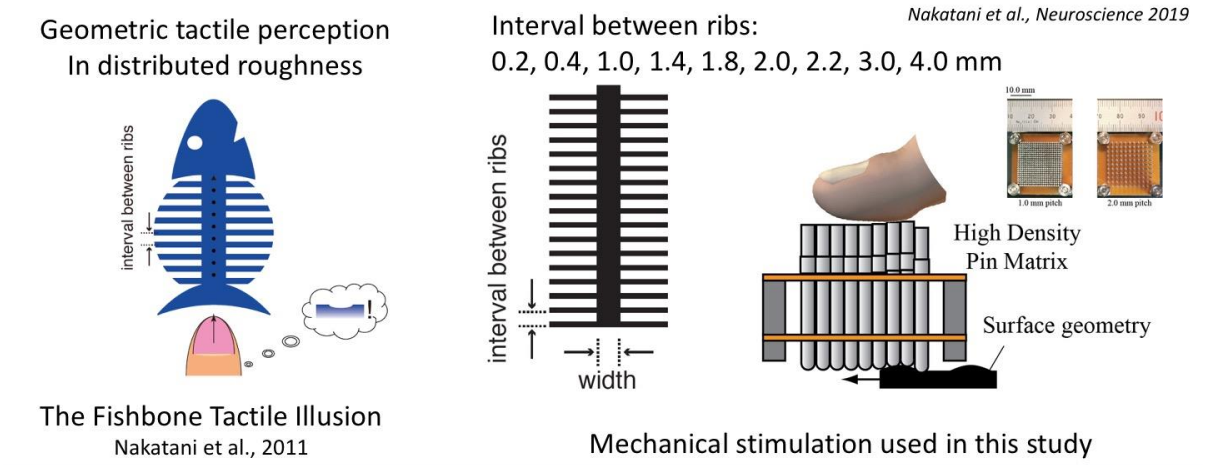
Topic: D.04. Somatosensation – Touch

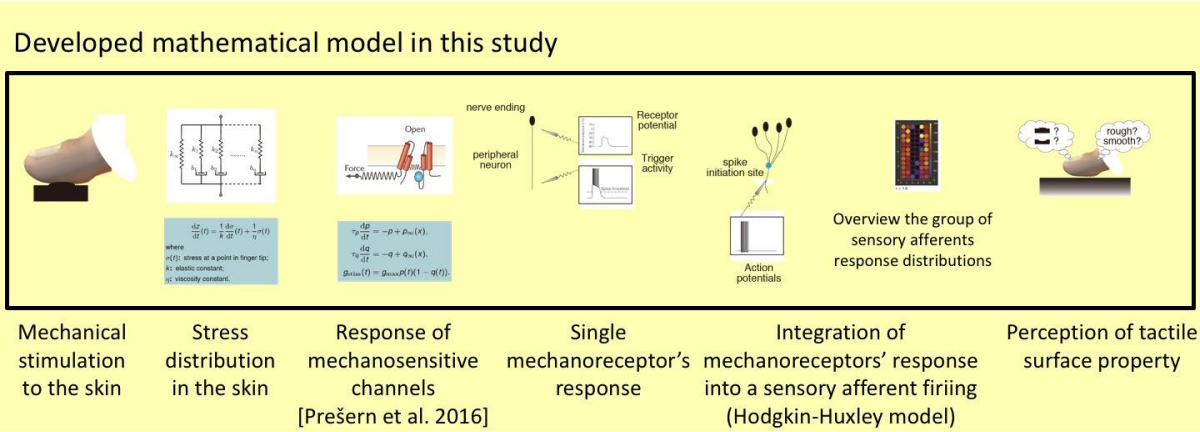
Support: JST CREST JPMJCR15D2
JST PRESTO JPMJPR16D7

Title: Both spatial and temporal patterns of sensory afferents activity may explain the geometric perception in the fishbone tactile illusion

Authors: *M. NAKATANI[1], M. UESAKA[2], S. MOGAMI[1], Z. ZHAO[2], T. SUSHIDA[2], H. KITAHATA[3], M. NAGAYAMA[2];
[1]Keio Univ., Fujisawa, Japan; [2]Hokkaido Univ., Sapporo, Japan; [3]Chiba Univ., Chiba, Japan

Abstract: We study whether both spatial and temporal information encoded in the sensory afferents could be utilized to recognize tactile surface roughness and geometric features. For this purpose, we employed a known tactile phenomenon called the Fishbone Tactile Illusion (FTI) [Nakatani et al., 2011]. This illusion occurs with an archetypal surface geometry, which has a smooth central bar and textures (ridges and grooves) in its adjacent areas. By stroking the central bar back and forth with the skin of a fingertip, an observer typically perceives an indented surface geometry although the bar is physically flat. The credibility of indented geometric perception produced by the FTI is high, but its neural mechanism is still elusive. In order to address possible mechanisms of the geometric perception, we used a passive high-density pin matrix to extract only vertical information of the contact surface and to exclude tangential force caused by rubbing the surface. In the psychophysics experiment, the participants reported an indented surface geometry by moving over the FTI texture of nine different inter-ridge spacing with pin matrices of two different densities (1.0 and 2.0 mm pin intervals, 0.8 mm of pin diameter). However, the participants significantly decreased the answering rate of indented perception in a certain condition. In this condition, pins in the adjacent areas vibrated in synchronization, suggesting a different perceptual mechanism of interpreting tactile surface roughness. To look at this phenomenon in detail, we developed a mathematical model that can simulate tactile signal processing from a mechanical stimulus to geometric perception. Our mathematical simulation result suggests that (1) humans may utilize precise timing of sensory afferents responses as suggested in the previous study [Pruszynski and Johansson 2014] and (2) both spatial and temporal phase distributions of firing frequencies of sensory afferents would be utilized in the perception of the FTI.





Disclosures: **M. Nakatani:** None. **M. Uesaka:** None. **S. Mogami:** None. **Z. Zhao:** None. **T. Sushida:** None. **H. Kitahata:** None. **M. Nagayama:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.07

Topic: D.04. Somatosensation – Touch

Support: Chinese NSF 81600982
National Natural Science Foundation of China 81520108010

Title: Correlation between the spatial-temporal parameters and tactile speed perception

Authors: *B. QU[1], M. XIN[1], T. SHEN[2,3,4], B. ZHANG[3,4], H.-Y. LAI[1,2,3,4];
[1]Col. of Biomed. Engin. and Instrument Science, Zhejiang Univ., Key Lab. for Biomed. Engin. of Ministry of Educ., Hangzhou, China; [2]Zhejiang Univ. Sch. of Medicine, Zhejiang Univ., Interdisciplinary Inst. of Neurosci. and Technol., Hangzhou, China; [3]Zhejiang Univ. Sch. of Medicine, Zhejiang Univ., Dept. of Neurol. of the Second Affiliated Hosp., Hangzhou, China; [4]Zhejiang Univ. Sch. of Medicine, Zhejiang Univ., Key Lab. of Med. Neurobio. of Zhejiang Province, Hangzhou, China

Abstract: Speed is one of the most important information to discriminate on a moving object among the attributes of tactile stimulus. Speed sensation involves co-varied multiple parameters including temporal frequency and spatial information. It has been demonstrated that speed and surface characteristics is confounded in the afferents. However, the tactile speed perception underlying this process remain poorly understood with co-varied multiple parameters. The goal of the study was to explore which features of tactile stimulus modify the extent of speed perception. To this end, we used lab-designed ball tactile stimulator to present a series of stimulus at the center of subjects' left index finger pad. The stimulation parameters included 4 wavelengths and 6 speed levels of motion. Subjects directly drew a line on the touchpad to response the scanning speed. All 29 subjects (18-35 years old) volunteered to participate in current study. The results collected from different wavelength balls were fit to polynomial curve fitting model, and the R^2 values were close to 1. According to the polynomial fitting function, the perceived speed could be positively correlated with scanning speed and the growth rate of perceived speed could be negatively correlated with wavelength. Although the results showed polynomial curve fitting model, the perceived speed also showed the linear correlated with stimulus frequency when the stimulus frequency lower than 60 Hz. In summary, the frequency was the main factor in the speed process and the wavelength also took part in the higher speed sensation with a negatively effect in the polynomial fitting function that indicated tactile speed perception was not a simple intensity process linearly. We will further investigate the mechanism of tactile speed encoding with co-varied multiple parameters by using the electrophysiological recording and functional MRI in nonhuman primate.

Disclosures: **B. Qu:** None. **M. Xin:** None. **T. Shen:** None. **B. Zhang:** None. **H. Lai:** None.

Nanosymposium

358. Tactile Coding in the Cortex

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Topic: D.04. Somatosensation – Touch

Support: German Research Foundation, Special Research Field (Sonderforschungsbereich) 974 Project B07

European Union's Horizon 2020 research and innovation programme, Marie Sklodowska-Curie grant agreement No 795998 (MSCA-IF-GF awarded to T.J.B.).

Title: Neuronal oscillatory activity and temporal perception in the tactile domain - Alterations in hepatic encephalopathy

Authors: *T. J. BAUMGARTEN[1,2], M. LAZAR[2], N.-D. FÜLLENBACH[3], M. S. JÖRDENS[3], D. HÄUSSINGER[3], A. SCHNITZLER[2], J. LANGE[2];
[1]New York Univ. Langone Med. Ctr., New York, NY; [2]Inst. of Clin. Neurosci. and Med. Psychology, Med. Fac., [3]Dept. of Gastroenterology, Hepatology and Infectiology, Med. Fac., Heinrich Heine Univ. Düsseldorf, Düsseldorf, Germany

Abstract: The perceptual separation of successively presented tactile stimuli into temporally distinct sensations is tightly linked to neuronal oscillatory activity in low frequency bands (Baumgarten et al., 2015). However, it remains to be shown if neuronal oscillatory activity is altered in cases where tactile temporal perception is impaired. Hepatic encephalopathy (HE) is a major clinical complication in patients with liver cirrhosis. In addition to motor and neuropsychological impairments (Jones & Weissenborn, 1997), HE patients also demonstrate perceptual deficits. While decreases in visual temporal resolution are well-described and can be quantified by a standardized parameter, the critical flicker frequency (Kircheis et al., 2002), recent publications have shown that HE patients also show deficits in tactile temporal perception (Lazar et al., 2018). This allows for the possibility to investigate neuronal oscillatory activity linked to temporal perception in the tactile domain in a patient sample where tactile perception is impaired. Here, we investigated the relationship between tactile temporal resolution and different measures of oscillatory brain activity in patients with varying grades of HE (minimal HE / manifest HE) and healthy controls.
18 controls (12 male, 62 +/- 12 y) and 13 HE patients (9 male, 58 +/- 9 y) performed a tactile temporal discrimination task in which two suprathreshold electrical stimuli with varying stimulus onset asynchrony (SOA; 0-400 ms) were presented to the left index finger. Subjects reported if they perceived the stimulation as one single or two temporally separate sensations. Whole-head neuromagnetic activity was recorded and oscillatory activity in the alpha and beta bands were compared across groups.
Compared to controls, HE patients reported to perceive a single stimulus significantly more often for SOAs between 125-200 ms. For trials with these SOAs, HE patients showed a significant decrease in prestimulus beta band power (22-28 Hz; $p = 0.03$, corrected for multiple comparisons), with effects located in central and anterior sensors. In addition, HE patients showed significantly decreased alpha band peak frequencies in various parietal and temporal sensors ($p < 0.05$).
The present study demonstrates that perceptual impairments in HE go beyond the visual domain. Importantly, the current findings link disease-specific deficits in tactile temporal discrimination to established parameters of oscillatory activity connected to both tactile temporal sampling in healthy subjects (Baumgarten et al., 2015), as well as temporal resolution in visual perception (Samaha & Postle, 2015; Baumgarten et al., 2018).

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Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.09

Topic: D.04. Somatosensation – Touch

Support: NHMRC Grant APP1028284
Australian Government Research Training Program Scholarship

Title: Multiplexing intensity and frequency information using temporal pattern encoding of peripheral afferent nerve stimulation

Authors: ***K. K. W. NG**[1,2], I. N. SNOW[1,2], I. BIRZNIEKS[1,2], R. M. VICKERY[1,2];
[1]Sch. of Med. Sci., UNSW Sydney, Sydney, Australia; [2]Neurosci. Res. Australia, Sydney, Australia

Abstract: Temporal features of spike trains play an important role in the neural coding of stimulus information. Recent research from our laboratory has found that vibrotactile frequency perception depends on the duration of silent gaps between spike bursts, regardless of the number of spikes within the burst (Birznieks & Vickery, 2017, Current Biology). We exploited this knowledge in the current study, to investigate the contribution of the number of spikes within a burst to perception of vibrotactile intensity. We were able to vary the evoked mean spike rate during stimulation while keeping perceived frequency of the stimulus constant.
Patterns of spike trains were evoked in tactile afferents using mechanical or electrical stimulation on the fingertip. The stimuli were organised into bursts of impulses that repeated at a rate of 27 Hz. The number of impulses within a burst was varied from 2 to 4, all contained in the burst envelope of 13.5 ms. A total of 22 human subjects (aged 19-26, 11 females) participated across two psychophysical experiments, which had been approved by the UNSW Human Research Ethics Committee (HC16245). Mechanical stimuli were presented at 30 µm, while electrical stimulation was conducted at currents just below the pain threshold of subjects (5.5-7.5 mA). Where mechanical stimulation was used, subjects listened to pink-noise through headphones to mask auditory cues. The psychophysical method of magnitude estimation was used to determine subjects' perceived intensity. Intensity ratings were performed against a fixed standard which was trains of 2-spike bursts. Linear regression revealed that the mean spike rate had a significant effect on perceived intensity during electrical stimulation (slope = 0.47, 95% CI 0.41-0.54; R^2 =

0.82; P < 0.0001). For mechanical stimuli, this effect was substantially smaller (slope = 0.08, 95% CI 0.04-0.11; R^2 = 0.32; P < 0.0001).
The marked difference between the evoked intensity using mechanical and electrical stimulation points to a possible role for afferent type or spatial pattern of afferent activity, in intensity perception. The slowly adapting afferents would be effectively activated by the electrical but not the mechanical stimulation. Electrical stimulation also results in a spatial pattern of activation that differs from that produced by a natural mechanical stimulus. These findings raise the possibility of a stimulation scheme that could encode both frequency and intensity information in the temporal patterning of impulses delivered by nerve stimulation for prosthetic hands in amputees.

Disclosures: K.K.W. Ng: None. **I.N. Snow:** None. **I. Birznieks:** None. **R.M. Vickery:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.10

Topic: D.04. Somatosensation – Touch

Support: ARC Grant DP170100064

Title: Active movements from the fingers are required to consciously perceive surface friction during object manipulation

Authors: *N. AFZAL[1,3], H. KHAMIS[2,3], E. STUBBS[1,3], M. WIERTLEWSKI[4], S. J. REDMOND[5], R. M. VICKERY[1,3], I. BIRZNIEKS[1,3];
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Abstract: Successful manipulation during precision gripping with the human hand requires frictional information. It has been observed that the grip forces are adjusted to both the destabilizing load forces and the frictional conditions between the object and the skin when using a precision grip. This adjustment to the frictional conditions appears to be achieved without any exploratory or sliding movement of the fingers on the object surface. We used a two-alternative forced choice protocol to examine human capacity to tell which of two presented smooth surfaces is more slippery in a passive touch condition, when surfaces were brought in contact to the immobilized fingers by a robotic manipulator. An ultrasonic friction modulation device was used to render three levels of friction (high, medium and low friction) of the glass. Passive touch was tested with and without net tangential force. When no net tangential force was present, subject performance was at chance level (47±13%) (mean correct ± SD; n=17). When adding a

net tangential force (approach angle 20° to the normal), subject performance remained at chance level (50±15%) (mean correct ± SD). To test whether active movement commands are required to access frictional information we tested an active touch condition in which subjects actively moved their fingers to touch the stationary surface of the friction modulation device. Two conditions were tested: when the hand rested on a support to minimize finger tangential movement, and free movement without a support. The subjects' overall performance with the hand resting on a support was still at chance level (68 ± 15%) (mean correct ± SD; n=12). In contrast, subjects could easily tell which surface was more slippery when the hand could move freely without a support (88 ± 8%) (mean correct ± SD; n=12). This study demonstrated that unrestrained active movement is a key for humans to perceive frictional properties of a smooth surface. Friction-dependent fingertip deformation patterns do not seem to translate into perception of frictional properties. This suggests that fingertip movements upon object approach may induce subtle sliding over the surface before safe contact is established, and that these play a key role in friction sensing. However, it cannot be excluded that frictional information extracted from fingertip deformation pattern might be available for motor control but not for conscious perception.

Disclosures: N. Afzal: None. **H. Khamis:** None. **E. Stubbs:** None. **M. Wiertlewski:** None. **S.J. Redmond:** None. **R.M. Vickery:** None. **I. Birznieks:** None.

Nanosymposium

358. Tactile Coding in the Cortex

Location: Room S401

Time: Monday, October 21, 2019, 1:00 PM - 3:45 PM

Presentation Number: 358.11

Topic: D.04. Somatosensation – Touch

Support: Facebook, Inc, USA

Title: Tactile emojis and the language of social touch

Authors: *S. MCINTYRE[1], R. BOEHME[1], S. C. HAUSER[3], A. KUSZTOR[1], A. MOUNGOU[2], G. NOVEMBRE[4], G. J. GERLING[5], P. M. ISAGER[6], A. ISRAR[7], S. S. NAGI[1], F. ABNOUSI[7], E. A. LUMPKIN[8], M. BJORNSDOTTER[1], H. OLAUSSON[1];
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Abstract: Touch is a powerful communication tool, but it is underused in technology-mediated interactions such as teleconferencing; one reason being our limited understanding of the neural,

behavioral, and physical features of social touch. Within close relationships, we found that touchers intuitively conveyed distinct emotional messages that receivers could identify. Imaging the receiver's brain, specific messages were most distinguishable in the somatosensory cortex, consistent with affective touch processing there. Emotional engagement in the form of concurrent facial expression was not necessary for successful communication. Furthermore, trained touchers using standardized touch gestures that we developed, were readily understood by naïve strangers. Thus, the view emerges of a universal language of social touch represented in the somatosensory cortex; an insight that can guide the development of social haptic interfaces.

Disclosures: **S. McIntyre:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **R. Boehme:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **S.C. Hauser:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **A. Kusztor:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **A.**

Moungou: 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **G. Novembre:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **G.J. Gerling:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **P.M. Isager:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **A. Israr:** A. Employment/Salary (full or part-time):; Facebook. **S.S. Nagi:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **F. Abnousi:** A. Employment/Salary (full or part-time):; Facebook. **E.A. Lumpkin:** F. Consulting Fees (e.g., advisory boards); Facebook. **M. Bjornsdotter:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook. **H. Olausson:** 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.; Facebook. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Facebook.

Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.01

Topic: G.02. Motivation

Support: DFG Grant INST 392/115

Title: Topographically segregated signals in the amygdala mediate the integration of hedonic values into food choices

Authors: L. J. TIEDEMANN[1], A. ALINK[2], J. BECK[1], C. BUECHEL[1], ***S. BRASSEN**[1]; [1]Dept. of Systems Neurosci., [2]Dept. for Systems Neurosci., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Introduction and Methods: When we are hungry and body energy levels are low, we have to eat to satisfy nutritional needs. Many individuals, however, do not only eat for metabolic reasons, but also for pleasure. Previous research has unraveled the neurocircuits underlying food decisions, and those underlying valence coding, but how valence signals are integrated into food choices has been less addressed. Given the amygdala's central location within a dense neural network transferring food- and feeding relevant information, we applied pattern-based representational similarity and effective connectivity analyses to amygdala signals acquired while overnight fasted normal-weight volunteers performed an explicit palatability valuation task on food stimuli on one day and a consumption decision task on the same food items on another day. Results and Conclusions: Our multivariate analysis showed that during the explicit valuation of food cues, spatial amygdala patterns differentially coded for the whole range of valence. Interestingly, such valence specific activation patterns could also be identified during consumption decisions. Further exploration of voxel-wise amygdala activity patterns suggested topographically segregated amygdala subareas which differentially incorporated appetitive and aversive liking values into the accumbal-prefrontal valuation network during food choices. Using the independently identified valence-specific amygdala patterns as an indicator for single-item valence processing during consumption decisions, we were able to predict the impact of food liking on food choices on a trial-by-trial basis. Our findings translate very recent animal data on appetitive and aversive amygdala subsets into the human brain (Wang et al., *Nature* 2017) and may help to understand the mechanisms of how hedonic food valuation can mediate eating decisions.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.02

Topic: G.02. Motivation

Support: New York Stem Cell Foundation; Robertson Neuroscience Investigator
NIH Director's New Innovator Award
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Brain and Behavior Research Foundation; NARSAD Young Investigator Award
Cornell Neurotech; Mong Junior Fellowship
Cornell University

Title: Tonic excitation in lateral habenula promotes adaptive termination of goal pursuit and threat avoidance

Authors: *B. J. SLEEZER, R. J. POST, D. A. BULKIN, V. LEE, M. R. WARDEN;
Cornell Univ., Ithaca, NY

Abstract: Neurons in the lateral habenula (LHb) are excited by punishments and omitted rewards and the LHb is often viewed as the brain's punishment or disappointment center. Recent research suggests that the LHb also plays a role in flexible decision-making and effort, but the role of LHb in shaping behavior in different motivational contexts is not fully understood. Here, we investigate the dynamics and functional role of LHb neurons in disengagement from goal pursuit and threat avoidance. We injected cre-dependent AAV-GCaMP6s into the LHb of klk8-Cre mice and implanted an optical fiber over the LHb to monitor activity-dependent fluorescence. We recorded LHb activity during a task in which mice were required to perform a nose-poke to receive a reward. Each successful nose poke yielded a large reward on 20%, a medium reward on 60%, and no reward on 20% of trials. As expected, LHb activity increased following reward omission and decreased following medium or large rewards. Intriguingly, we also observed a tonic increase in LHb activity as mice disengaged from the task toward the end of each daily session as they became sated ($r = 0.1369$, $p < 0.0001$, Pearson correlation). When mice performed a version of the task in which reward and no-reward blocks were alternated, we found that LHb activity peaked during task disengagement in no-reward blocks and decreased upon resumption of task performance during reward blocks ($p = 0.0127$; paired samples t-test). We repeated these experiments while recording multiunit electrical activity and observed similar results. Next, we optogenetically inhibited LHb during task performance and found that mice completed more trials when LHb was inhibited compared to when it was not ($p = 0.0316$, paired samples t-test). Finally, we examined multiunit LHb activity while mice attempted to escape from a rapidly moving robot cricket into a small cardboard hut, but were blocked from entering. Similar to our findings in the poke-reward task, we found that LHb multiunit activity increased when mice ceased attempts to escape into the hut after multiple failures. These results reveal tonic excitation of LHb neurons during adaptive termination of behavior in both positive and negative motivational contexts; upon successful resolution of homeostatic needs, upon the termination of reward pursuit after repeated reward omission, and upon the cessation of escape attempts. These effects could not be explained by changes in running speed and were observed in both population calcium activity and multiunit electrical activity. These findings suggest that tonic excitation in LHb promotes cessation of behavior in positive and negative motivational contexts.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.03

Topic: G.02. Motivation

Support: BIAL Foundation Grant (PT/FB/BL-2016-030)
Norte 2020 (NORTE-01-0145-FEDER-000013)
FCT (POCI-01-0145-FEDER-007038)

Title: Role of different laterodorsal tegmentum to nucleus accumbens inputs in reward

Authors: *B. COIMBRA[1,2], C. SOARES-CUNHA[1,2], A. V. DOMINGUES[1,2], S. BORGES[1,2], N. A. P. VASCONCELOS[1,2], N. SOUSA[1,2,3], A. J. RODRIGUES[1,2,3];
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Abstract: Mesopontine neurons of the laterodorsal tegmentum (LDT) send specific inputs that tightly modulate the activity of dopaminergic neurons of the ventral tegmental area (VTA), controlling the release of dopamine in the nucleus accumbens (NAc), a core region of the reward circuit. Until recently, NAc acetylcholine was believed to originate exclusively from striatal cholinergic interneurons, but direct projections from the LDT to NAc have been recently described, though their functional role remains to be determined. Therefore we investigated the role of LDT-NAc projections using a combination of anatomical, and functional studies. The majority of LDT-NAc inputs are cholinergic, although there is also GABAergic and glutamatergic innervation. LDT drives mainly an excitatory net response in the NAc. We further show that optogenetic activation of LDT-NAc projections in rats enhances motivational drive and shifts preference to an otherwise equal reward; whereas inhibition of these projections induces the opposite. Additionally, specific activation of LDT-NAc cholinergic inputs (but not glutamatergic nor GABAergic inputs) is sufficient to shift preference, increasing motivational drive, and to drive positive reinforcement in different behavioral paradigms. These results extend the knowledge on how the LDT is able to contribute for reward-related behaviors either by direct control of NAc activity or indirectly through the VTA.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.04

Topic: G.02. Motivation

Support: 1R01MH106689-01A1

Title: Midbrain dopamine neurons contribute to spatial working memory during the delay period

Authors: *J. CHOI[1,2], H. JANG[1], S. ORNELAS[1], J. AU[3], I. B. WITTEN[1,2];
[1]Princeton Neurosci. Inst., [2]Dept. of Psychology, [3]Dept. of Mol. Biol., Princeton Univ., Princeton, NJ

Abstract: Although dopamine had been implicated in working memory on long time scales (through pharmacology), the role of the fast temporal dynamics of activity in dopamine neurons (on the order of seconds) is not clear. This is a big gap in knowledge because working memory is inherently fast, with multiple phases (updating, maintenance, motor readout). Thus, it is not clear which component of working memory is being influenced by neuromodulators. By recording activity in VTA and SNc dopamine neurons with fiber photometry, we found that activity was elevated during the updating and motor execution of working memory, but not the delay period. However, optogenetic manipulation of dopamine neurons affected working memory most severely during the delay period, compared to the other periods. Both increasing and decreasing dopamine neurons during the delay period impaired working memory, consistent with classic ideas that the relationship between dopamine and working memory obeys an inverted U-shaped curve, and that there is an optimal level of dopamine during the delay period. This effect could be attributed to the VTA dopamine neurons, while SNc dopamine neurons were more implicated in the motor readout. This work provides evidence regarding which dopamine neurons are needed, and when, to support spatial working memory.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.05

Topic: G.02. Motivation

Support: NIH T32

Title: Medial and lateral VTA DA neurons have distinct temporal control during fear extinction

Authors: *L. X. CAI[1], K. PIZANO[2], G. GUNDERSEN[2], C. HAYES[2], W. T. FLEMING[2], S. HOLT[2], H. WANG[2], I. B. WITTEN[2];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Princeton Univ., Princeton, NJ

Abstract: The primary view of dopamine (DA) in learning is that bursts of DA encode a reward prediction error (RPE), which updates the value of preceding or concurrent events. However, whether DA neurons can also alter behavior or drive learning to events subsequent to a burst of activity is less clear. Thus, we use fiber photometry and optogenetics to examine the timescale of DA's impact on fear extinction. This behavior enables a continuous readout of learning (freezing). It also allows us to examine the consistency of RPE coding during the extinction of negative associations, complimenting previous work which focused on the formation of positive associations. To automate the readout of freezing, we employ a convolutional neural network to the behavioral videos. This new approach eliminates the need to manually score videos in which the mouse's neural headgear movement confounds traditional freezing detection algorithms. We find that medial ventral tegmental area (VTA) DA neurons have a burst of activity at the tone offset during extinction and inhibiting this activity slowed extinction learning, consistent with an RPE-like signal. In contrast, the more prominent feature of lateral VTA DA neurons during fear extinction is a burst at the tone onset and not offset, which may signify salience. Inhibiting lateral VTA neurons at the tone onset also slowed extinction learning, despite the absence of a typical RPE signal. In both subregions, inhibiting the tone offset increased freezing during the inter-tone-interval after the inhibition period, an effect that increased over extinction. This suggests that DA neurons can affect behavior after a burst of activity, in addition to or instead of providing a reinforcement signal to strengthen the previous stimulus or action. This is contrary to classic models relating DA activity and learning, and opens up new interpretations regarding the function of non-RPE signals that have been increasingly recognized to be present in some DA neurons.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

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Presentation Number: 359.06

Topic: G.02. Motivation

Support: NIH BRAIN Initiative U01-NS103470
NIH Grant R01-DA038642
Stanley Fahn Research Fellowship

Title: Local and global consequences of reward-evoked striatal dopamine release

Authors: *N. LI, A. JASANOFF;
Biol. Engin., MIT, Cambridge, MA

Abstract: The neurotransmitter dopamine is required for the reinforcement of actions by rewarding stimuli. Neuroscientists have tried to define dopamine's functions in concise conceptual terms, but the practical significance of dopamine release depends on its diverse brain-wide consequences. Although the molecular and cellular effects of dopaminergic signaling have been extensively studied, its impact on larger-scale neural activity profiles is less understood. Here we combine dynamic dopamine-sensitive molecular imaging and functional magnetic resonance imaging (fMRI) to determine how striatal dopamine release shapes local and global responses to re-warding stimulation in the rodent brain. We find that dopamine consistently alters the duration but not the magnitude of stimulus responses across much of striatum, via quantifiable postsynaptic effects that vary across subregions. Striatal dopamine release also potentiates a network of distal responses we delineate using neurochemically-dependent functional connectivity analyses. Hot spots of dopaminergic drive notably include cortical regions associated with both limbic and motor function. Our results thus reveal distinct neuromodulatory actions of striatal dopamine that extend well beyond its sites of peak release, and that result in enhanced activation of remote neural populations necessary for performance of motivated actions. Our findings also suggest brain-wide biomarkers of dopaminergic function and provide a basis for interpreting human and animal neuroimaging results relevant to learning and addiction.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.07

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R21DA041600

Title: Understanding the molecular basis of nicotine addiction by integrative functional genomic analyses in a rat model and hiPSC-derived DA neurons

Authors: *A. KOZLOVA[1,2], R. R. BUTLER, III[1,2], S. ZHANG[1,2], T. UJAS[2], M. STREIT[1], H. ZHANG[1], A. R. SANDERS[1,2], Z. PANG[3], S. STEIDL[4], P. V. GEJMAN[1,2], P. VEZINA[2], J. DUAN[1,2];
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Hlth. Inst. of New Jersey, Rutgers Univ., New Brunswick, NJ; [4]Dept. of Psychology, Loyola Univ. Chicago, Chicago, IL

Abstract: Cigarette smoking is the largest preventable risk factor for mortality and a primary risk factor for many chronic diseases. Tobacco consists of more than 4,800 compounds, among which nicotine is responsible for the addictive nature of smoking. Repeated exposure to nicotine leads to sensitization, enhancing its self-administration and that of other drugs. We aimed to identify translatome and transcriptome profiles in nicotine addiction-relevant rat brain regions [ventral tegmental area (VTA); nucleus accumbens (NAc)] and in dopamine (DA) neurons derived from human-induced pluripotent stem cells (hiPSCs). We used F1 progeny of F344 and BN rat strains to analyze nicotine associated translatome and trancriptome changes. Male and female F1s showed a dose-dependent increase in nicotine-induced locomotion; however, only males exhibited nicotine sensitization. We are now performing the translatome profiling of the F1s brains and determining whether these are similar to those observed in hiPSC-derived nicotine sensitized midbrain DA neurons. Compared to human postmortem brains from the Genotype-Tissue Expression (GTEx) and BrainSpan projects, these hiPSC-DA neurons showed a strong expression correlation with brain regions relevant to addiction. Interestingly, the DA neuron enriched midbrain showed the highest correlation with hiPSC-DA neurons for nicotine/DA-related genes, supporting the validity of hiPSC-DA neurons for the transcriptomic study of nicotine addiction. We also subjected the hiPSC-derived DA neurons to multi-electrode analysis. We were able to detect DA neuronal activity, and found that acute nicotine treatment increases neuronal firing. Preliminary sequencing results of ribosome protected RNA fragments from F1 brain tissues and DA neurons showed ~70% of reads mapped to ribosomal RNA (rRNA). We are currently optimizing a protocol to reduce the proportion of sequences that align to rRNA. Preliminary transcriptome analysis of nicotine sensitization in male F1s showed an association with NAc Core and 48 differentially expressed genes compared to saline exposed controls. Interestingly, expression of these genes is lower in GTEx brain samples, suggesting altered expression associated with sensitization. Finally, nicotine self-administration showed transcriptional association with the VTA region of the brain. Identifying novel gene targets relevant to NIC addiction will increase understanding of the neurobiology of human NIC abuse and inform the development of more effective therapeutics.

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Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

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Topic: G.02. Motivation

Support: BBSRC Standard Grant BB/P003427/1
EU COST ACTION CA15120 Open Multiscale Systems Medicine (OpenMultiMed)

Title: Can neuromodulatory neural circuits be degenerate? A theoretical investigation of serotonin-dopamine interaction in conditioning tasks

Authors: C. K. BEHERA[1], A. JOSHI[1], D.-H. WANG[2], T. SHARP[3], ***K. WONG-LIN**[1]; [1]Intelligent Systems Res. Ctr., Ulster Univ., Derry~Londonderry, United Kingdom; [2]State Key Lab. of Cognitive Neurosci. and Learning, and Sch. of Syst. Sci., Beijing Normal Univ., Beijing, China; [3]Dept. of Pharmacol., Univ. of Oxford, Oxford, United Kingdom

Abstract: Degeneracy is the ability to perform the same function or output despite being structurally different. An advantage of degeneracy in neural circuits is the stable and robust maintenance of network function in the face of network structural changes or variability. It is well known that brain functions can be modulated by chemical neuromodulators, leading to cognitive and behavioural changes. However, it is unclear whether the neuromodulator system can themselves consist of degenerate neural circuits, leading to stable neuromodulatory effects. In this theoretical study, we address this issue by focusing on modelling the direct and indirect interactions between two well-studied neuromodulators, serotonin and dopamine. Specifically, we build on our previous mean-field modelling approach and develop a neural circuit model consisting of the ventral tegmental area (VTA) and dorsal raphe nucleus (DRN) in rewarding-/aversive-based conditioning tasks. The network model activity is constrained by recent optogenetic studies in these brain regions. To test for degeneracy, we restrict the activities of any DRN-VTA circuit model to some prescribed activity profile based on common observations in recent optogenetic and electrophysiological studies during conditioning tasks. Then, the structure of the DRN-VTA network is systematically altered. Each version of the DRN-VTA model always consists of the same afferent input structure and neuronal populations (5-HT neurons, DA neurons, glutamatergic neurons in DRN, GABAergic neurons in DRN, and GABAergic neurons in VTA). We prescribe a maximal deviation range on the simulated activity profile and the desired profile at every time bins. Only network architectures that lie within this prescribed tolerance range are considered. Based on the model simulations, we identify twelve different network architectures that can produce the same activity profile. Applying dynamical systems theory, the stability of these degenerate networks are found to be stable. Then, we simulate D2 receptor agonist effects in these degenerate DRN-VTA networks, and with increasing dosage level, we can gradually distinguish the sub-groups of network architectures based on their differential responses to the agonist. Overall, this work suggests the plausibility of degeneracy in the DRN-VTA neuromodulatory circuit and has important implication on the stable and robust maintenance of neuromodulation.

Disclosures: C.K. Behera: None. **A. Joshi:** None. **D. Wang:** None. **T. Sharp:** None. **K. Wong-Lin:** None.

Nanosymposium

359. Subcortical Circuitry in Reward, Motivation, and Aversion

Location: Room S505

Time: Monday, October 21, 2019, 1:00 PM - 3:15 PM

Presentation Number: 359.09

Topic: B.09. Network interactions

Support: Deutsche Forschungsgemeinschaft (AM 488/1-1)
NARSAD Young Investigator Award

Title: Plasticity of glutamatergic inputs onto medium spiny neurons during polypharmacy cross-sensitization

Authors: *D. AMATO, A. KRUYER, J. PARRILLA-CARRERO, E. DERESCHEWITZ, P. W. KALIVAS;
Med. Univ. of South Carolina, Charleston, SC

Abstract: D1 and D2 medium spiny neurons (MSNs) in the nucleus accumbens core (NAc) differently mediate the rewarding properties of cocaine and other drugs of abuse. Using *in vivo* Ca^{2+} miniature microscopic imaging we have measured the activity of population of neurons in the direct (D1 MSNs) and indirect (D2 MSNs) pathways and have shown that the cocaine-induced locomotor sensitization is produced by activation of a larger proportion of NAc D1 and deactivation of D2 MSNs activity. The pre-exposure of mice to chronic haloperidol treatment, a traditional antipsychotic used in schizophrenia, enhanced the locomotor sensitization to cocaine at a much higher level than the behavior observed after the sole exposure to cocaine. This increased sensitivity to the psychostimulatory effects of cocaine induced by the pre-exposure to the antipsychotic was associated to a simultaneous activation of the direct and indirect pathways. Suggesting that the co-activation of the D1- and D2- MSNs are necessary to increase the stimulatory effects of psychostimulants likely driven by an unbalanced dopamine-glutamate neurotransmission between presynaptic and postsynaptic neurons in the NAc. We inquired into the cellular nature of glutamate being triggered by haloperidol which activated the indirect pathway bypassing the inhibitory control of dopamine. Accordingly, the NAc glutamate background increased with haloperidol and is reflected in electrophysiological recordings of D2-MSNs and by astroglial morphological adaptations that promote glutamate spillover. This study has relevance to understand substance use disorder in patients with mental disorders, such as schizophrenia, with a history of polypharmacy.

Disclosures: D. Amato: None. **A. Kruyer:** None. **J. Parrilla-Carrero:** None. **E. Dereschewitz:** None. **P.W. Kalivas:** None.

Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

Location: Room N427

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 360.01

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant ZIA-DA000587

Title: Complementary task structure representations in the hippocampus and orbitofrontal cortex during performance of an odor sequence task

Authors: *J. ZHOU[1], M. MONTESINOS-CARTAGENA[1], A. WIKENHEISER[1], M. GARDNER[1], Y. NIV[2], G. SCHOENBAUM[1];
[1]Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Both hippocampus (HPC) and orbitofrontal cortex (OFC) have been shown to be critical for behavioral tasks that require the use of an internal model or cognitive map of the environment or task. One general idea is that the HPC serves up this map, and the OFC transforms it to emphasize relationships that are relevant to current goals. Our previous analysis of ensemble activity in OFC in rats performing a familiar odor sequence task revealed a rich representation of behaviorally-relevant task structure, consistent with this proposal (Zhou et al., Curr Biol, 2019). The odor sequence task was designed to resemble a spatial maze. On each trial, rats sampled one of 16 odors and made a "go" or "no-go" response to obtain a reward or to avoid a prolonged inter-trial-interval (ITI), and to continue to the next "location" (odor) in the "maze". The 16 odors were organized into two pairs of 6-trial odor sequences (S1a vs. S1b and S2a vs. S2b), with the last four odors in each pair being identical (shared). In sequences S1a and S1b, the shared odors made identical reward predictions, whereas in sequences S2a and S2b, some made opposing predictions, depending on the context (i.e., depending on previous odors in the sequence, that determined whether this was sequence S2a or S2b). Together, the odor sequences provided a mappable state space, with 24 "positions" defined by sensory information, likelihood of reward, or both. Here we compared those data from OFC to recordings from single units in CA1 of HPC in rats performing the same odor sequence task. Contrary to our expectation that HPC ensembles would represent detailed, even incidental, relationships defining the full task space, we found that HPC ensembles recorded in well-trained rats failed to distinguish locations (states) where such a distinction was not behaviorally necessary and performed even worse than OFC ensembles at rewarded positions. However, hippocampal ensembles represented task states when the rats made transitions from explicit to hidden states better than did OFC neurons. These results suggest that at least in familiar environments, HPC and OFC play complementary roles, with the orbitofrontal cortex maintaining the subjects' current position in a global framework, supported by hippocampus when memory demands are high.

Disclosures: J. Zhou: None. **M. Montesinos-Cartagena:** None. **A. Wikenheiser:** None. **M. Gardner:** None. **Y. Niv:** None. **G. Schoenbaum:** None.

Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

Location: Room N427

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 360.02

Topic: H.01. Animal Cognition and Behavior

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R01 MH105427
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1I01BX001524-01A1

Title: Emergence and elimination of hippocampal odor/time-cell sequences and their link to working-memory

Authors: *J. TAXIDIS[1], E. PNEVMATIKAKIS[2], A. L. MYLAVARAPU[1], J. S. ARORA[1], P. GOLSHANI[1];
[1]UCLA, Los Angeles, CA; [2]Ctr. for Computat. Biol., Flatiron Institute, Simons Fndn., New York, NY

Abstract: Hippocampal circuits form representations of sensory inputs and time. Cell assemblies encoding such information generate spiking sequences which temporally organize experiences. But how do both sensory and time representations emerge and what is their link to a memory context?
We have recently shown that during an olfactory delayed non-match-to-sample task (DNMS), requiring working memory (WM), pyramidal cells in the mouse dorsal CA1 form odor-specific sequences, tiling the odor cue and delay period (Taxidis et al., bioRxiv, 2019). These sequences comprise of 'odor-cells', activated during the presentation of specific odor stimuli, followed by 'time-cells' spiking during specific time-points in the delay after a given odor. Odor-cells exhibit robust and stable spiking fields for multiple days and delay durations, whereas time-cell activity is sparse and dynamic, with time-fields remapping over days and delays.
These differences in the encoding regime for odor versus time, raise a series of questions. Do both these representations emerge as DNMS is learned or do such sequences pre-exist in the network? Are they linked to the WM context or can any odor stimulation trigger them? And do they causally drive WM activation?
We address these questions using *in vivo* two-photon calcium imaging on head-fixed mice, as well as optogenetic manipulations. We recorded activity from thousands of neurons over multiple days while mice learned the DNMS task. We demonstrate that during learning, the number of odor-cells remained stable whereas the number of time-cells increased. This increase

was not observed during passive DNMS-exposure in naïve mice, indicating that a WM-context is required for time-cell emergence. After mice reached well-trained stages, they were passively exposed to randomly timed odor stimuli. Interestingly, outside the DNMS task context, the number of odor- and time-cells dropped to chance levels, suggesting that WM-activation is required for sustaining these sequences even after they formed.
Finally, we optogenetically inhibited either CA1, medial entorhinal cortex (MEC) or lateral (LEC) during learning the task. We observed no behavioral effects when inhibiting CA1 suggesting that these sequences do not drive WM. However, inhibiting MEC resulted in slower learning curves compared to controls, while LEC inhibition completely prohibited learning of the task.
This work indicates that sensory/time sequences emerge in CA1 during learning of a WM context and are eliminated outside that context. However, they appear to reflect upstream computational processes in entorhinal cortex that support learning.

Disclosures: **J. Taxidis:** None. **E. Pnevmatikakis:** None. **A.L. Mylavarapu:** None. **J.S. Arora:** None. **P. Golshani:** None.

Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

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Presentation Number: 360.03

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP 1839287
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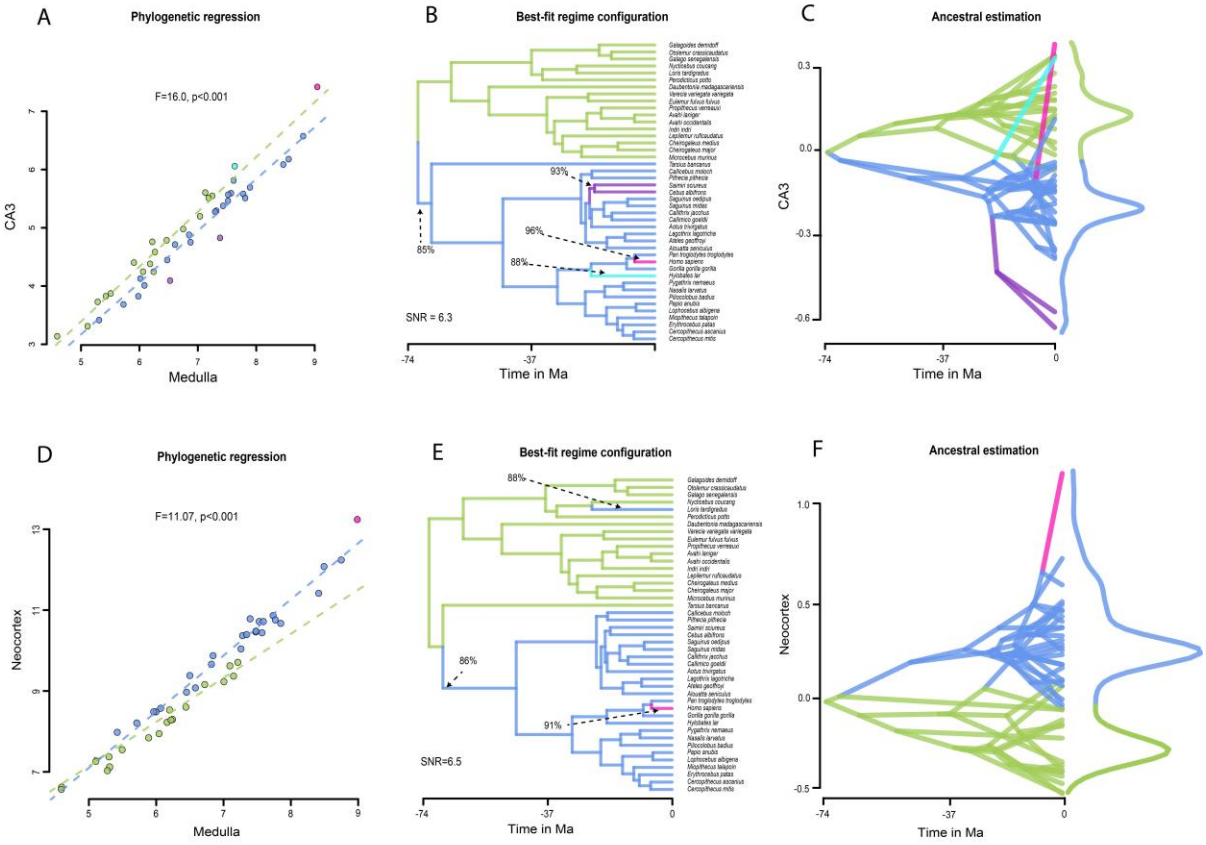
Wenner Gren 9209

Title: The evolution of hippocampal formation subregions in primates

Authors: *D. VANIER[1], C. SHERWOOD[3], J. SMAERS[2];
[1]IDPAS, [2]Stony Brook Univ., Stony Brook, NY; [3]Anthrop., George Washington Univ., Washington, DC

Abstract: As the hippocampal formation (HF) represents the spatial and temporal details of experience, comparative studies of its structure are pivotal to understanding how representational memory evolved in humans. Virtually nothing, however, is known about the evolutionary changes that occurred in the HF subregions in humans and our closest relatives. We investigated the changes in the size of hippocampal subregions (CA1, CA2, CA3, DG, subiculum, rhinal cortex) across 43 primate species, and compared the evolution of the hippocampal subregion sizes to the neocortex. Volumetric data in mm^3 were gathered from the literature. Subregions

were first delineated on slices of 10-20 µm thickness, and areas were transformed into volumes. Subregion volumes were scaled against the medulla. This provides a robust cross-species measure preferable to absolute size (which can vary with brain size). Relative sizes and data on the relatedness of species were used as input for Bayesian evolutionary models. These models detect where in the phylogeny changes in the mean value (shifts) in relative HF subregion size may have occurred. A phylogenetic least squares ANOVA was used to confirm whether certain groups of species (shifts predicted by the evolutionary model) statistically differed in mean relative HF subregion size. Apes and monkeys (*blue*) display decreases in relative CA3 ($p < 0.001$), DG ($p < 0.001$), subiculum ($p < 0.01$), and rhinal cortex ($p < 0.01$) in tandem with an increase in relative neocortex ($p < 0.001$) compared to the ancestral state. Humans (*pink*) uniquely combine increased relative CA3, subiculum, and rhinal cortex with an increased relative neocortex. Our results imply that HF subregions underwent selection for different functional roles, although the evolutionary pattern of individual subregions defies simple functional explanations. In apes and monkeys, a relative decrease in several HF subregions may be due to augmentation of representational memory by an expanded neocortex. In humans, a relative increase in several HF subregions may play a role in our enhanced episodic-memory.



Disclosures: D. Vanier: None. **C. Sherwood:** None. **J. Smaers:** None.

Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

Location: Room N427

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 360.04

Topic: H.01. Animal Cognition and Behavior

Title: During remote recall anterior cingulate cortex theta improves hippocampal contextual processing

Authors: *R. A. WIRT, J. M. HYMAN;
Psychology, Univ. of Nevada Las Vegas, Las Vegas, NV

Abstract: Given the singular role that memory plays in all behavior, decoding the neural circuits underlying memory storage and recall is vital. Soon after memory formation, recall of contextual information is dependent on the hippocampus (HC), but as memories become more remote, recall becomes independent of the medial temporal lobes. Multiple lines of research have shown that the anterior cingulate cortex (ACC) is involved with contextual information processing and remote recall of contextual memories. We reasoned that if this is the case, then these changes should cause shifts in neuronal ensemble and network oscillatory activity between the ACC and hippocampal area CA1. To assess this, we recorded single units and local field potentials from the ACC and CA1 while animals were exposed to a series of unique environments and then re-exposed to those same environments at differing time delays (1-14 days). Behavioral data revealed subjects quickly became familiar with the environments, with discernable changes to exploratory activity occurring as early as the second exposure. During remote recall ACC-CA1 theta coherence increased, with ACC theta leading area CA1. Theta band communication from the ACC also regulated CA1 unit spike timing, gamma oscillations, along with ensemble and single neuron information coding in CA1. In fact, for CA1 ensembles the degree of ACC theta entrainment was predictive of how strongly that population differentiated one context from another. Over the course of consolidation, the strength and prevalence of ACC theta modulation grew, leading to richer environmental context representations in CA1. Thus, we have discovered a novel electrophysiological marker of consolidated memory recall and these results will force a reconsideration of how long term memory readout transpires.

Disclosures: R.A. Wirt: None. **J.M. Hyman:** None.

Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

Location: Room N427

Time: Monday, October 21, 2019, 1:00 PM - 2:45 PM

Presentation Number: 360.05

Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (31522028, 81571056, 2014NT15)
National Key Basic Research Program of China (973 Program, 2014CB744600)
Thousand (Young) Talents Program of China
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the Fundamental Research Funds for the Central Universities

Title: Stress-sensitive cortisol awakening response optimizes hippocampal and prefrontal circuitry to support emotion memory suppression

Authors: *C. BIAN[1,2,3], W. LIN[1,2,3], L. ZHUANG[1,2,3], B. XIONG[1,2,3], S. QIN[1,2,3];
[1]State Key Lab. of Cognitive Neurosci. and Learning, [2]IDG/McGovern Inst. for Brain Res., [3]Beijing Key Lab. of Brain Imaging and Connectomics, Beijing Normal Univ., Beijing, China

Abstract: The cortisol awakening response (CAR), a prominent increase in cortisol levels following morning awakening, is a reliable index of hypothalamic–pituitary–adrenocortical axis activity. The CAR has profound impacts on brain systems critical for human memory and higher-order cognitive functions. Abnormality of the CAR has been linked to stress-related mental disorders. However, little is known about the neurobiological mechanisms of how the CAR modulates human memory systems. Using event-related fMRI with Think/No-think and consolidation paradigm, we investigated how the CAR affects suppression of emotional memory before and after consolidation, as well as its associated neural substrates. Sixty-seven young healthy men participated this study while they performed Think/No-think task for emotional memories acquired either 30-minute (newly-acquired) or 24-hour (remote/consolidated) before. Saliva samples were collected at 6-time point to access CAR and diurnal rhythms of cortisol levels. Behaviorally, individual's CAR could proactively predict suppression-induced forgetting for newly-acquired but not consolidated emotional memories, with better suppression-induced forgetting in normal than blunted CAR groups. On neuroimaging level, we found that individual's CAR could proactively predict neural activity in the bilateral hippocampus, with higher hippocampal activity in normal than blunted CAR groups. Further analysis revealed a significant interaction effect between Group (Normal vs. Blunted) and newly-acquired emotional memory (No-Think vs. Think) in the left hippocampus. That is, individuals with normal (relative to blunted) CAR showed hyper-activation in suppression of newly acquired emotional memories (but not retrieval). Interestingly, we also observed significant interaction effect on hippocampal functional connectivity with the inferior frontal gyrus, with higher connectivity in normal than blunted CAR groups in suppression of newly acquired emotional memories. Our findings suggest that human CAR could proactively prime the brain into an optimal state to support suppression of emotional memories, through its modulatory roles on the hippocampus and related functional circuits in the prefrontal cortex.

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Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

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Presentation Number: 360.06

Topic: H.02. Human Cognition and Behavior

Support: the National Natural Science Foundation of China (31522028, 81571056, 2014NT15)
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Title: Stress-sensitive cortisol awakening response proactively augments hippocampal-prefrontal functional organization in humans

Authors: *B. XIONG[1,2,3], C. CHEN[4], Y. TIAN[1,2,3], S. ZHANG[5,6], C. LIU[1], J. WU[7], S. QIN[1,2,3]; [1]State Key Lab. of Cognitive Neurosci. and Learning, [2]IDG/McGovern Inst. for Brain Res., [3]Beijing Key Lab. of Brain Imaging and Connectomics, Beijing Normal Univ., Beijing, China; [4]Sch. of Educational Sci., Xinyang Normal Univ., Xinyang, China; [5]West Essence Clinic, Beijing Inst. of Functional Neurosurg., [6]Xuanwu Hosp., Capital Med. Univ., Beijing, China; [7]Shenzhen Key Lab. of Affective and Social Cognitive Sci., Shenzhen Univ., Shenzhen, China

Abstract: The cortisol awakening response (CAR), a burst in cortisol concentrations within 20-30 minutes following morning awakening, superimposes unto the daily rhythm of hypothalamus-pituitary-adrenal axis activity. The CAR appears to be an important feature distinct from the basal circadian cortisol secretion and cortisol reactivity to acute stress. Empirical evidence from human behavioral research has linked individual differences in CAR with a wide range of affective and cognitive functions. Deviations from a typical CAR pattern are also linked to mental disorders such as anxiety and depression. However, the neurobiological mechanisms underlying the modulatory effects of CAR on human brain functions remain to be illustrated. Across two studies, we employed functional magnetic resonance imaging (fMRI) in conjunction with pharmacological manipulation of the CAR to investigate how CAR modulates prefrontal and hippocampal functions in humans. In Study 1, we explored the relationship between CAR and the neurocognitive correlates of working memory (WM) in a natural setting. Salivary samples of 60 young healthy men were obtained at 6-time points to assess CAR and diurnal rhythms of cortisol levels. Brain imaging data were acquired when participants performed a numerical N-back WM task with low and high task demands in the afternoon of the same day. Individuals with blunted CAR, whose cortisol level increased less than 50% at 30 minutes after awakening, showed a general hyper-activation in the hippocampus regardless task demands, and specific hyper-activation in the dorsal lateral prefrontal cortex (dlPFC) and disrupted coupling between the hippocampus and the dlPFC only for high task demand. In Study 2, by leveraging a randomized, double-blinded, placebo-controlled design, we investigated the causal link of CAR

with brain activity during WM task. Sixty-three young healthy men orally received either a dose of 0.5-mg Dexamethasone or an equal amount Vitamin C pill at 20:00 on Day 1. Participants completed a similar N-back WM task during fMRI scanning in the afternoon on Day 2. A total of 15 saliva samples were collected through 3 consecutive days, with concurrent monitoring of participant's subjective mood by the positive and negative affection scale. Suppression of CAR by DXM resembled our observed effects in the hippocampus and dlPFC from Study 1 on the experimental day, without alternation of cortisol level before and after fMRI scanning as well as affective dynamics over 3 experimental days. Our findings suggest that the CAR proactively reorganizes human hippocampal and prefrontal functional circuits into an optimal state to support executive functions.

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Nanosymposium

360. Learning and Memory: Cortical-Hippocampal Interactions

Location: Room N427

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Presentation Number: 360.07

Topic: H.01. Animal Cognition and Behavior

Support: Alzheimer's Association Grant SAGA-17-418745

Title: Thalamus-hippocampal direct pathway regulates sex-differences in memory consolidation

Authors: *G. TORROMINO[1,2], V. LOFFREDO[1,3], F. ESPOSITO[4], M. COLUCCI[4,2], M. DE RISI[2], M. GIOFFRÈ[5], E. DE LEONIBUS[1,2];
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Abstract: Human and rodent studies amply reported that sex-differences regulate the hippocampal (HP) recruitment in memory tasks. However, the neuronal bases of these sex-differences are unknown.
We have identified a new sexual dimorphism in memory consolidation when animals are specifically tested in high memory load conditions. By a combination of c-fos brain mapping, chemogenetics and optogenetics approaches we report here that inactivation of the thalamic-HP pathway rescues HP activation and memory consolidation impairment in female mice. Inhibition of the same pathway has no detectable effects on consolidation in male mice.
These findings identify for the first time a bottom-up negative regulatory control of sub-cortical-

thalamic regions on HP activation in female compared to male mice that leads to failure in memory consolidation.

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Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.01

Topic: H.02. Human Cognition and Behavior

Title: Agency affects the emotional outcome and the neural correlates of social decisions

Authors: M. GÄDEKE[1], T. WILLEMS[2], O. SALAH[3], B. WEBER[3], R. HURLEMANN[4], ***J. W. SCHULTZ**[3];
[1]Bonn Neurosci. MSc Program, [2]Neurosci. MSc Program, [3]Ctr. for Econ. and Neurosci., Univ. of Bonn, Bonn, Germany; [4]Psychiatry and Med. Psychology, Univ. Clin. Bonn, Bonn, Germany

Abstract: People are often required to take decisions for others or to accept a decision taken for them by others. To test if decision agency (i.e. who takes the decision) influences how one experiences the outcomes of a decision and to investigate the neural mechanisms underlying these experiences, we adapted a recently published social decision task (Rutledge et al, Nature Communications 2016) into the following paradigm. Participants in an fMRI scanner or a game partner repeatedly chose between a safe and a risky option in a gamble for money. If the risky option was chosen, the gamble was played out independently for both players, such that both could either win or lose the gamble. Participants reported momentary happiness after experiencing the outcome. We found that negative outcomes for one or both players led to lower happiness ratings if participants rather than their opponent made the decision. Neural activation reflected agency during decision-making: taking the decision themselves involved brain areas associated with gamble evaluation as well as with empathy, whereas being passively exposed to the partner's decision engaged areas associated with Theory of Mind. Furthermore, activation in superior temporal gyrus varied with participants' overall life happiness: Happier subjects showed greater effects of agency on the neural responses in this region than less happy participants. These results show that agency influences both the emotional outcome and the neural correlates of social decision-making, and that some of these neural correlates are sensitive to inter-individual variation in life happiness.

Disclosures: M. Gädeke: None. **T. Willems:** None. **O. Salah:** None. **B. Weber:** None. **R. Hurlemann:** None. **J.W. Schultz:** None.

Nanosymposium

361. Decision Making

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Presentation Number: 361.02

Topic: H.02. Human Cognition and Behavior

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the Thousand Young Talents Program of China

Title: Multivariate neural representations of multiple decision uncertainties in human anterior cingulate cortex

Authors: W. JIA[1,2], ***J. SU**[1,2], X. WAN[1,2];
[1]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China;
[2]IDG/McGovern Inst. for Brain Res. at BNU, Beijing, China

Abstract: Metacognition is a form of cognitive control with decision uncertainty as the control signal. The dorsal anterior cingulate cortex (dACC) has been believed to encode abstract control signals in cognitive control across different tasks. However, it remains unclear how domain-generic control signals in the dACC could elicit domain-specific behavioral control in the prefrontal cortex. We here investigated the neural representations of multiple decision uncertainties accompanying three different decision-making tasks in the domains of perception, rule-based inference and memory using trial-by-trial univariate and multivariate analyses. We found that dACC correlated with decision uncertainties of tasks from three different domains at the voxel-wise level, indicating that the intensity of decision uncertainties in dACC should be domain-generic. Using MVPA, we found that dACC also encoded the task identity information of decision uncertainties, showing that decision uncertainties in dACC are also domain-specific. By decomposing the neural activities into different components, we found that multivariate neural activities associated with decision uncertainty in the dACC concurrently encoded the identity and intensity information of control signals in two dissociated components through the neural activity patterns and magnitudes. To further test the domain-generic and domain-specific representations of decision uncertainties in dACC, we investigated the influence effects from another preceding decision-making task. Our behavioral results confirmed that the decision uncertainty from the preceding task only affected the confidence report, but not the decision-making per se. Hence, our findings suggest that the mosaic neural representations of decision uncertainty in the dACC during metacognition should be both domain-generic and domain-specific, guiding appropriate cognitive control for different domain decision-making tasks. The

feature of domain-generic encoding of decision uncertainty in dACC also provides a neural account for the influences of confidence or "confidence leak" between interleaved tasks, or even between different domains.

Disclosures: W. Jia: None. **J. Su:** None. **X. Wan:** None.

Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.03

Topic: H.02. Human Cognition and Behavior

Title: Hexadirectional coding in human entorhinal cortex represents the trajectory through social networks during decision-making

Authors: *S. A. PARK, D. S. MILLER, E. D. BOORMAN;
Ctr. for Mind and Brain, Univ. of California, Davis, Davis, CA

Abstract: Recent findings suggest the hippocampal-entorhinal (HPC-ERC) system may serve a general mechanism for representing and navigating cognitive maps of non-spatial tasks. These map-like representations can be used to guide flexible goal-directed behavior. However, it is unclear whether the HPC-ERC system uses the same organizational principles to map the dimensions of abstract and discrete problems. We, therefore, developed a novel task to test how human brains map non-spatial, discrete dimensions and use this representation to guide decision-making. Participants learned the relationship between 16 entrepreneurs in two independent ability dimensions by comparing two entrepreneurs' relative rank in a hierarchy. During fMRI participants were asked to choose the better of two partners for a given entrepreneur by comparing their joint 'growth potential (GP)'. The GP corresponded to the area drawn by the relative rank of two entrepreneurs in the 2-dimensional cognitive space. We found that the level of dissimilarity of HPC-ERC activity patterns increased with the Euclidean distance between entrepreneurs in the 2-D social network. Moreover, ERC and ventromedial prefrontal cortex (vmPFC) encoded the difference in GP between the pairs, suggesting a role in guiding decision-making. Finally, we show that the HPC-ERC system and vmPFC display hexadirectional signals, which serve as a proxy measure for a grid-like code, representing the trajectories through the cognitive space. This grid-like signal is consistent across sessions acquired more than a week apart. Our findings suggest a general grid-like code in human ERC that is extended to encode trajectories in abstract and discrete problems that serve everyday decision-making.

Disclosures: S.A. Park: None. **D.S. Miller:** None. **E.D. Boorman:** None.

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361. Decision Making

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Support: National Center for Responsible Gaming
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Title: The role of frontal dopamine in risky decision-making in gambling addiction

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Abstract: Gambling disorder is the prototypical behavioral addiction, and is associated with impairments in decision-making and cognitive control. Compared to healthy controls, gamblers exhibit increased temporal discounting and risk-taking (Wiehler & Peters, 2014). Dysregulation in the dopamine (DA) system has been implicated in various forms of addiction, including gambling. Here we examined whether increasing frontal dopamine levels via the catechol-O-methyltransferase (COMT) inhibitor Tolcapone would modulate risk-taking behavior in a sample of n=14 problem and pathological gamblers in a randomized, double-blind, placebo-controlled within-subjects study. On each day, participants performed 112 trials of a risky choice task (Peters & Büchel, 2009) involving reward probabilities between 0.1 and 0.99. Data were fit via a hierarchical Bayesian estimation scheme using JAGS (Plummer, 2003). Following recent developments in reinforcement learning (Pedersen et al., 2017; Fontanesi et al., 2019), values were linked to choices either via a standard softmax choice rule or to both choices and reaction times via the drift diffusion model (DDM) using the Wiener module for JAGS (Wabersich & Vandekerckhove, 2014). Risk-preferences modeled via a hyperbolic probability discounting model showed very good correspondence between softmax and DDM choice rules both for the baseline (placebo) data (r=.95) as well as the tolcapone-induced shift in risk-preferences (r=.85). Therefore, further analyses focused on the DDM model. Although Tolcapone increased risk-taking (directional Bayes Factor: 5.84), it also attenuated the non-decision time (directional Bayes Factor: 5.88), increased the boundary separation (directional Bayes Factor: 4.22) and attenuated the value-dependency of the drift rate (directional Bayes Factor: 4.87). Augmentation of prefrontal DA levels in gamblers modulates various facets of choice behavior involving both preferences and choice dynamics. We discuss these results in the context of models of the role of DA in gambling disorder.

Disclosures: J. Peters: None. **T.A. Vega:** None. **D. Weinstein:** None. **J. Mitchell:** None. **A.S. Kayser:** None.

Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.05

Topic: H.02. Human Cognition and Behavior

Support: ES/J500112/1
WT103184/Z/13/Z
MR/N014448/1
WT100973AIA
203139/Z/16/Z

Title: Polarity of subjective uncertainty in ventromedial prefrontal cortex changes with behavioural adaptation

Authors: *N. TRUDEL[1], M. K. WITTMANN[1], J. SCHOLL[1], M. KLEIN-FLÜGGE[1], E. FOURAGNAN[2], M. F. S. RUSHWORTH[1];
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Abstract: Environments typically furnish multiple information sources which might be used to make predictions about subsequent events of importance such as rewards. How do we select predictors that are useful? Here we describe this process at behavioural and neural levels. First, we show that during early encounters with potential predictors, participants' selections were explorative and directed towards uncertain predictors. This is particularly the case when the time horizon is long and many future opportunities remain to exploit the knowledge that is gained. However, a preference for accurate predictors increased over time, as did a tendency to pick certain predictors. We then describe how this transition is governed by representations of belief uncertainty in ventromedial prefrontal cortex (vmPFC) using Bayesian modelling and functional magnetic resonance imaging. Activity in vmPFC was sensitive to participants' (un)certainty in their beliefs about predictors but the polarity of uncertainty representations (positive or negative encoding of uncertainty) changed with the behavioural mode: an uncertainty decision signal was present during exploration, while activity in the same region signalled certainty during exploitation. Although the dichotomy between exploration and exploitation has often been treated as binary, we show that periods of uncertainty and certainty representation in vmPFC are separated by a transitional period in which beliefs about predictors' accuracy predominate in their impact on vmPFC activity. These findings suggest vmPFC carries information about a multiplicity of decision variables, the strength and polarity of which vary according to their relevance for the current context.

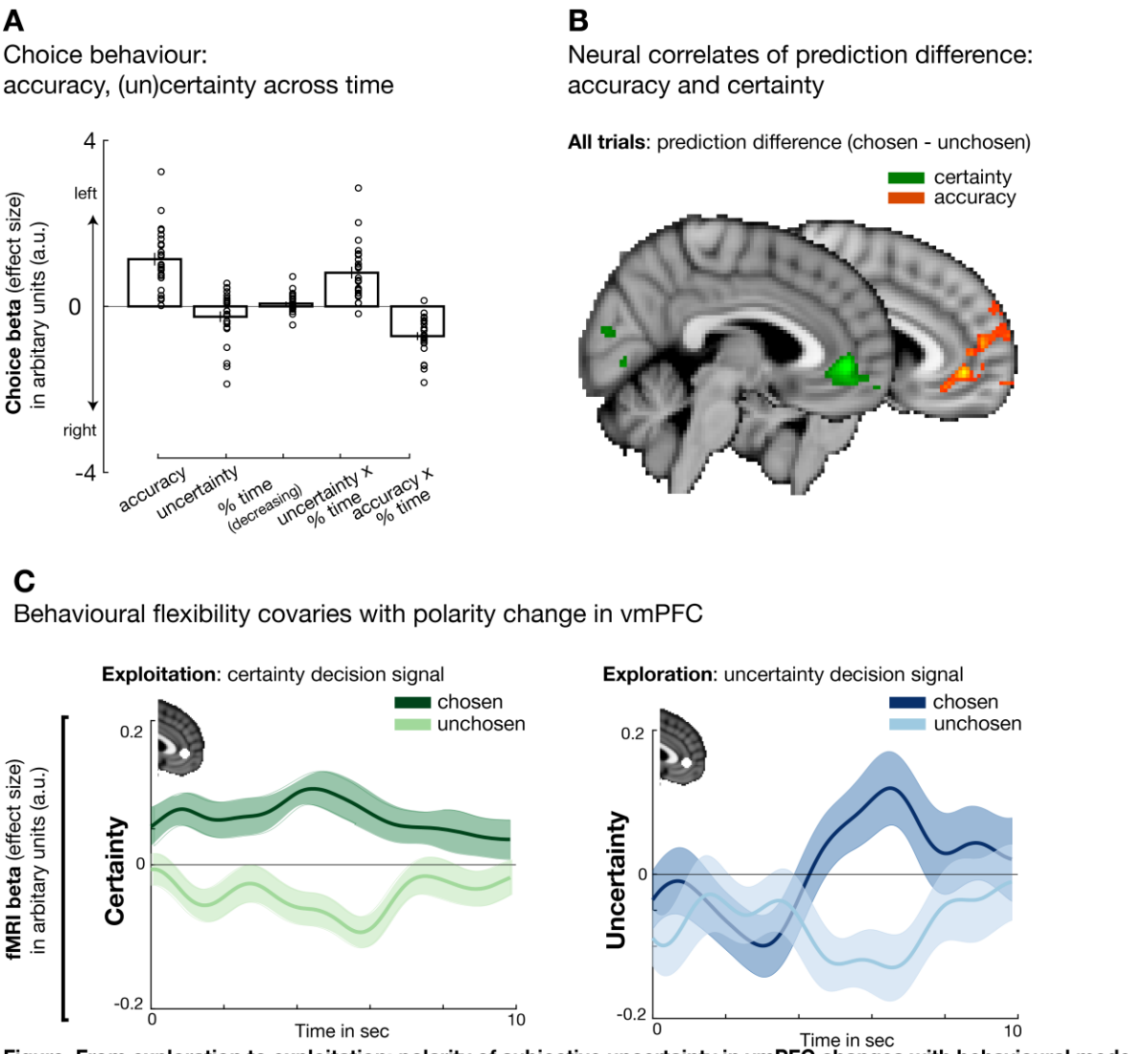

Figure. From exploration to exploitation: polarity of subjective uncertainty in vmPFC changes with behavioural mode. (A) Behavioural choices show that generally accurate predictors were preferred and uncertain ones were avoided. However, uncertainty and accuracy estimates exerted different effects depending on when choices were made: uncertain predictors were explored when many trials still remained (positive interaction term with % time), whereas decisions were accuracy- driven as the end of a block approached (negative interaction effect with % time). (B) Certainty (negative uncertainty effect) and accuracy prediction differences (contrast: chosen predictor certainty – unchosen predictor certainty) covaried with activation in vmPFC on average across all trials. (C) In accordance with these behavioural results, we found a similar change in vmPFC; it transitioned from having activity positively related to certainty difference (positively encoding the certainty of the chosen predictor as opposed to the unchosen predictor) during initial choices to having activity positively related to uncertainty difference (positively encoding the uncertainty of the chosen predictor as opposed to the unchosen predictor) in later trials. Illustration of time courses extracted from vmPFC for both chosen and unchosen components of a decision signal during exploitation (left panel) and exploration (right panel). vmPFC activation covaried with a decision signal that changed its polarity depending on the current behavioural mode: a certainty decision signal was represented during exploitation, while exploration required the representation of an uncertainty decision signal.

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Nanosymposium

361. Decision Making

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Presentation Number: 361.06

Topic: H.02. Human Cognition and Behavior

Support: JSPS Grant-in-Aid for Scientific Research B (17H04248)
MEXT Grant-in-Aid for Scientific Research on Innovative Areas (18H05130)

Title: Conservative and hasty decision styles are differently associated with static and dynamic functional connectivity in healthy and schizophrenia people

Authors: *J. MIYATA[1], A. SASAMOTO[1], T. EZAKI[2,3], N. MASUDA[4], Y. MORI[1], M. ISOBE[1], T. ASO[1], T. MURAI[1], H. TAKAHASHI[1,5];
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Abstract: Background
Humans need more evidence for decision making than rational thinking expects, known as the conservatism bias. On the other hand, people with schizophrenia and delusion need less evidence to make a decision than healthy people, known as the jumping to conclusions (JTC) bias. We investigated their neural correlates in healthy people (HP) and patients with schizophrenia (SCZ), using beads task and static / dynamic functional connectivity (FC) analysis of resting state functional magnetic resonance imaging (rsfMRI).
Methods
Thirty-four HP and 41 SCZ subjects performed the beads task: subjects were presented with jars A and B, containing 80 blue / 20 yellow and 20 blue / 80 yellow beads, respectively. Beads were drawn from one of the jars repeatedly, and subjects were asked to guess from which jars the beads were drawn. Large / small number of draws needed to decision (DTD) indicated conservative / hasty decisions.
The rsfMRI data was acquired on a 3T scanner, and was analyzed using independent component analysis. Following networks of interest (NOIs) were identified: the default mode networks (DMNs), central executive networks, salience network, medial temporal lobe network, basal ganglia network and thalamus.
For static FC analysis, within- and between-network FC analyses were performed using subject specific spatial maps and time courses, respectively.
For dynamic FC analysis, subject-specific time courses were analyzed by energy landscape analysis (ELA), based on pairwise maximum entropy model. Transition rate between stable and unstable brain states was calculated.

Both static and dynamic FC were tested with diagnosis by DTD analyses of covariance, with age, gender, IQ and temporal SNR of rsfMRI data as covariates ($p<0.05$, corrected for voxels, contrasts and networks).
Results
Within-network analysis showed no significant results.
Between network analysis showed a significant interaction between diagnosis and DTD, indicating that reduced static connectivity between anterior and posterior DMNs was correlated with bigger DTD in HP and smaller DTD in SCZ.
ELA showed stable brain states were characterized by activation and deactivation of almost all NOIs, while unstable states were characterized by activation and deactivation of salience-related NOIs. A significant interaction was found between diagnosis and DTD,
indicating more frequent transition was correlated with bigger DTD in HP, while this relationship was diminished in SCZ.
Discussion
This study revealed static and dynamic neural correlates of conservatism and JTC biases in HP and SCZ. These findings elucidate the pathway from decision making to psychotic symptom such as delusion.

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Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.07

Topic: H.02. Human Cognition and Behavior

Title: Uncovering the neural underpinnings of semantic similarity judgments

Authors: *M. IORDAN[1], C. ELLIS[3], D. N. OSHERSON[2], J. D. COHEN[1];
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Abstract: Similarity judgments are a fundamental component of our interaction with the world, helping us to relate new stimuli to previously learned categories and thereby generalize learned behaviors to novel situations. However, it remains unclear how commonality of features and the attention we afford them gives rise to perceptual similarity for real-world objects (Tversky & Hemmenway, 1984; Osherson et al., 1991) and the neural underpinnings of this process are even less well understood (Keung et al., 2016). Here, we hypothesized that directing attention to task-relevant features of semantic categories involves the modulation of high-level sensory cortices by control mechanisms in prefrontal cortex in a manner that reflects changes in perceptual

judgments (Miller & Cohen, 2001; Cukur et al., 2013). To test this hypothesis, we conducted a pilot fMRI experiment (n=4) in which participants were asked to judge the similarity of animals, first in an unconstrained manner, and then along two behaviorally salient dimensions (furriness and predacity). Judgments were made among eight basic-level animals, presented in pairs of short naturalistic videos. Perceptually, feature-cued similarities predicted unconstrained similarity very well (r=0.84). Neurally, the representational similarity structure elicited during the feature-cued tasks also predicted the structure elicited by unconstrained similarity judgments across visual (LO: r=0.61), semantic (entorhinal: r=0.51), parietal (IPS: r=0.56), and frontal regions (PFC: r=0.61). Furthermore, we found that neural distances between semantic concepts predicted behavioral judgments in high-level visual cortex (LO: r=0.26), but less so in parietal (IPS: r=0.11) and frontal regions (PFC: r=0.02). Simultaneously, the identity of the relevant attended feature (e.g., furriness) was recoverable from multivariate patterns in parietal and frontal cortices (MVPA decoding accuracy: IPS 70%, PFC 78%; $p<0.01$), which suggests that representations in visual cortex may be influenced by top-down attentional modulation of activity in prefrontal and/or parietal cortex in an online fashion. Together, our results provide preliminary evidence that neural distances between concepts change in occipito-temporal cortex as a function of task-relevant control signals expressed in frontal and parietal cortices. Understanding this process will afford us a new window into how cognitive control operates under the constraint of moment-by-moment perceptual demands.

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Nanosymposium

361. Decision Making

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Presentation Number: 361.08

Topic: H.02. Human Cognition and Behavior

Support: Start-up funds to T.D. from Texas Tech University

Title: Associative retrieval modulates causal attributions in retrospective revaluation

Authors: *S. O'BRYAN[1], E. J. LIVESEY[2], D. A. WORTHY[3], T. DAVIS[1];
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Abstract: Retrospective revaluation is a phenomenon in human causal learning whereby individuals update their beliefs about previously encountered cues on the basis of continued experience with associated cues. Both theoretical and computational models of retrospective revaluation predict that causal attributions for such stimuli are updated via associative retrieval processes, but how and whether the brain supports revaluation in a manner consistent with

associative retrieval is currently undetermined. In this experiment, we tested the associative retrieval hypothesis using multi-voxel pattern analysis of fMRI data and an allergy prediction task known to elicit revaluation behavior. Participants were first trained to predict whether an allergic reaction would occur in a hypothetical patient exposed to different animal-food stimulus pairs (e.g., Cat + Strawberry = Allergic Reaction). In a second learning stage, animals and foods from the initial stage were presented individually, with outcomes that either agreed or conflicted with previous learning (Strawberry = No Reaction). Revaluation was then assessed during a test phase where participants rated the likelihood of a reaction to the unpresent but associated stimuli from phase two (Cat). To measure the reactivation of associated cues, independent localizer scans were collected to distinguish between multi-voxel patterns associated with each object class. Our results revealed that neural similarity to unpresent, but associated cues during the second learning phase tracked individual differences in revaluation behavior at test, where greater neural similarity to the unpresent cues predicted stronger cue revaluation. Moreover, activation of the left frontal pole during feedback presentation was associated with behavioral measures of revaluation. These results are the first to provide direct neural evidence for the long-held theory that associative memory retrieval supports retrospective revaluation.

Disclosures: **S. O'Bryan:** None. **E.J. Livesey:** None. **D.A. Worthy:** None. **T. Davis:** None.

Nanosymposium

361. Decision Making

Location: Room S404

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Presentation Number: 361.09

Topic: H.01. Animal Cognition and Behavior

Support: NIMH MH062349
ONR Grant N00014-17-1-2041

Title: A macroscopic gradient of value and choice representations in a large-scale model of the multi-regional mammalian cortex

Authors: *U. PEREIRA, X.-J. WANG;
Ctr. for Neural Sci., New York Univ., New York City, NY

Abstract: Dopaminergic neurons encode reward prediction errors and guide reward-dependent (reinforcement) learning in the cortex. However, reward-dependent processing during decision-making remains poorly understood in a multi-regional, large-scale brain system. On the one hand, reward or value signals have been observed in many brain areas. On the other hand, there is experimental evidence suggesting that unsupervised Hebbian learning is pervasive across the cortex. Unsupervised Hebbian and reinforcement learning are qualitatively different classes of biological learning mechanisms. In unsupervised Hebbian learning, synaptic changes are driven

solely by the pre and post synaptic activity, while in reinforcement learning are also dependent on a global error signal carried by dopamine. In this work, we propose a local three-factor learning rule that continuously varies from unsupervised Hebbian learning to reinforcement learning along the cortical hierarchy. The central idea of a gradual shift from unsupervised learning to reinforcement learning is based on recent observation that dopamine receptor density (normalized by neural density) displays a systematic macroscopic gradient from sensory areas to higher association areas in the mammalian cortex. We implement this rule in a recurrent large-scale model of the cortex and explore the emergence of neural representations of value during a foraging decision-making task. In this task, subjects make a series of choices between options associated with different reward probabilities, and choice behavior displays the matching law. Mouse, Marmoset, Monkey and Human connectivity data were used to infer a principal axis of cortical organization and built a generative model for the cortical connectivity based on this principal axis in our network model. We use dopamine receptor density and gene-expression data to introduce a parametric variation of synaptic plasticity form unsupervised learning to reinforced learning along this principal axis. We trained our network in a two-choice foraging task in which the average reward contingency is reversed in trial blocks. We find that the neural representation of value gradually emerges across trials during learning and is distributed across the cortex. We systematically explore the variation of the spatiotemporal profile of the neuronal representation of value along the cortical principal axis of the model and identify testable predictions. Overall, we provide a network model for the emergence of a spatiotemporal distribution of value and choice signals across the multi-regional mammalian cortex through learning.

Disclosures: U. Pereira: None. **X. Wang:** None.

Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.10

Topic: H.02. Human Cognition and Behavior

Support: NIA Grant R01AG057184

Title: Daily practice of heart rate variability biofeedback training affects brain activity during social decision making

Authors: P. NASSERI[1], K. NASHIRO[2], H. YOO[2], M. JUNGWON[3], C. CHO[2], S. BACHMAN[2], P. LEHRER[5], J. F. THAYER[6], C. CHANG[7], T. FENG[4], S. NARAYANAN[4], *M. MATHER[2,1,3];
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Univ., Piscataway, NJ; [6]Psychological Sci., Univ. of California Irvine, Irvine, CA; [7]Sch. of Engin., Vanderbilt Univ., Nashville, TN

Abstract: The ability to regulate emotions is critical in adaptive decision-making. Previous studies have shown that people's behavior in social decision-making is often influenced by emotions which conflicts with their self-interest. Having higher heart rate variability (HRV) has been associated with an array of positive mental health outcomes, including lower anger and hostility, better emotion regulation, and improved executive functions. Here we test the hypothesis that increasing HRV can improve social decision-making by enhancing medial prefrontal cortex (mPFC) control processes. In previous findings, mPFC was activated during emotion reappraisal in the ultimatum game. MPFC is also a key hub region associated with controlling HRV. Thus, we examined how increasing HRV in daily sessions of biofeedback affects activation of emotion regulation circuitry regions in a social decision-making task. Forty-seven individuals completed five weeks of HRV-biofeedback training to either increase (n=22) or decrease (n=25) their HRV during practice sessions. After completing the training phase, they played a multi-shot ultimatum game as responders while inside the fMRI scanner. Participants were informed that the ultimatum game included human-generated and computer-generated offers.

In the ultimatum game, it is in a participant's best interest to accept all offers. However, anger at unfair offers often leads participants to reject offers, especially when they are from humans rather than computers. Consistent with this typical pattern, participants in the HRV-decrease group rejected human-generated unfair offers more than similar computer-generated offers. In contrast, HRV-increase participants did not reject more unfair human offers than computer offers. While evaluating unfair offers, the HRV-increase group had higher activation of medial prefrontal cortex (mPFC)--with peak activation in the paracingulate cortex-- than the HRV-decrease group. This group difference appears to be driven by the HRV-increase group showing increased mPFC activity when they were viewing human-generated unfair offers, compared to the HRV-decrease group.

Our findings suggest that daily HRV increasing practice modulates emotion reappraisal when evaluating unfair offers. Thus, HRV-biofeedback training may alter social decision-making by enhancing medial prefrontal brain mechanisms involved in emotion regulation.

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Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.11

Topic: H.02. Human Cognition and Behavior

Support: Peter Bossaerts received financial support from the University of Melbourne through the R@MAP program

Title: The effects of dopaminergic psychostimulants on complex problem solving

Authors: *E. A. BOWMAN[1], D. R. COGHILL[2], C. MURAWSKI[1], P. L. BOSSAERTS[1];
[1]The Brain, Mind and Markets Laboratory, Dept. of Finance., [2]Departments of Pediatrics and Psychiatry, The Univ. of Melbourne, Parkville, Australia

Abstract: The role of dopaminergic systems, particularly the mesocorticolimbic dopaminergic pathways and their associated cortical projections, in decision-making and goal-directed behaviours has been of increased research interest in recent years. Medications that target these pathways are often used in disorders of attention and cognition, and are now also often diverted to non-medical, off-label, and illicit uses in the hope that they will enhance cognition and focus in healthy people. However, research to date reveals a mixed picture of efficacy in this aspect, particularly with regard to performance in higher-cognitive tasks.

We completed a repeated-measures, double-blinded, placebo-controlled single dose trial (PECO: ACTRN12617001544369, U1111-1204-3404) to examine the actions of three indirect dopamine agonists on complex problem-solving performance of healthy adults. Participants received 15 mg dextroamphetamine, 30 mg methylphenidate, 200 mg modafinil, or placebo, counterbalanced across 4 testing sessions. Each session was at least one week apart. In each session, participants completed sixteen trials of the Knapsack Task (eight unique instances presented twice each), and the CANTAB Simple and Five-choice Reaction Time, Spatial Working Memory, Stockings of Cambridge, and Stop Signal Tasks. The Knapsack Task is a NP-hard combinatorial optimisation task, requiring the participant to explore different combinations of items to discover an optimal (maximal) value solution under a specified weight and time constraint.

Mixed-effects modelling of the knapsack decision sequence data revealed that in general, participants took longer to submit solutions in the active drug conditions, yet were less likely to find the optimal solution. Participants who performed below-average with placebo explored more while in the active drug conditions. Yet their performance still decreased. Above-average participants reduced performance too, as they actually explored less. Initial choices, a good predictor of eventual performance in a trial, became more random under active drug conditions. Performance in the Knapsack Task correlated strongly with the CANTAB Spatial Working Memory Task strategy score.

These findings suggest that dopaminergic stimulant medications may increase healthy adults' motivation to spend more time and explore more combinations in pursuit of the solution to a computationally complex problem. However, this does not always result in enhanced performance because exploration becomes more random, which decreases performance.

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Commercial Interest or their Agents (e.g., speakers' bureaus); Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, Sunovion. F. Consulting Fees (e.g., advisory boards); Eli Lilly, Medice, Novartis, Oxford Outcomes, Shire, Viforpharma. **C. Murawski:** None. **P.L. Bossaerts:** None.

Nanosymposium

361. Decision Making

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Presentation Number: 361.12

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01-DA038106
NARSAD, Brain and Behavior Foundation

Title: Rule adherence increases the efficiency of decision-making

Authors: *B. EBITZ[1], J. TU[1], B. Y. HAYDEN[2];
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Abstract: Many decisions are made deliberatively; we integrate multiple, graded sources of information into judgments about what to do. However, we can also streamline decision-making by applying rules: simplified, guiding policies for linking states to actions. In theory, using rules could increase the efficiency of decision-making because not all features of the decision problem are rule-relevant, meaning that we can simplify the computations needed for rule-based decision-making. While the idea that rule-based decisions are a more efficient use of limited neural resources makes intuitive sense and aligns to our introspective experience, it has not been tested empirically.
Here, we asked 1) whether rule-based decisions are more efficient than deliberative decisions, and 2) whether this is due to distributed changes across decision-making regions or, alternatively, to a handoff in control from more deliberative regions to more automatic ones. We did this by recording single neuron activity in three brain regions linked to economic decisions during a task that encourages both rule-based and deliberative decisions. We focused on the orbitofrontal cortex (OFC, 115 cells), ventral striatum (VS, 103 cells), and dorsal striatum (DS, 204 cells) because each of these regions is causally implicated in either deliberative, effortful decision-making, or to efficient, automatic decision-making. To infer whether individual decisions were made according to a rule or not, we modelled sequences of decisions as the product of various latent decision-making policies, then inferred the most likely policy underlying each choice. This allowed us to contrast the neural correlates of physically identical decisions, made via either rule-based or rule-free computations.
We found that neuronal activity decreased during rule-based decisions, compared to rule-free decisions in all three regions. However, at the same time, there was more information about choice. Thus, rule-based decisions were made more efficiently than non-rule based decisions

across all three regions. However, this was not due to a functional handoff from deliberative to automatic decision-making regions. Instead, within each region, rule adherence warped population choice representations so that rule-relevant dimensions were expanded and rule-irrelevant dimensions were compressed. These results support the idea that one major benefit to using rules is an increase in the efficiency of decision-making, which occurs though distributed changes in the representations of choice options such that rule-relevant discriminations are facilitated at the expense of rule-irrelevant discriminations.

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Nanosymposium

361. Decision Making

Location: Room S404

Time: Monday, October 21, 2019, 1:00 PM - 4:15 PM

Presentation Number: 361.13

Topic: G.02. Motivation

Title: Neural dynamics underlying the integration of reward and efficacy during evaluation and motivation of cognitive control

Authors: *R. FRÖMER[1], H. LIN[2], C. K. DEAN WOLF[1], M. INZLICHT[2], A. SHENHAV[1]; [1]Cognitive, Linguistic, and Psychological Sci., Brown Univ., Providence, RI; [2]Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: People typically find cognitive control effortful, but the mechanisms by which they choose how to invest this effort are poorly understood. To investigate this question, previous research has focused on the role of expected rewards in determining control allocation. However, a recent model of cognitive control points to an overlooked aspect of this decision process: to what extent is effort necessary for obtaining these rewards (i.e., how efficacious is one's effort)? This model predicts that expected reward and efficacy should be integrated to determine the expected value of control (EVC), and therefore influence neural activity at evaluation and selection stages of control allocation, and subsequent task performance. To test this prediction, we orthogonally manipulated reward and efficacy in a cued Stroop task while recording EEG, allowing us to dissociate their effects on incentive evaluation, control allocation, and performance. Consistent with our model's predictions, participants performed better at the task (were faster and/or more accurate) not only when there was a potential for greater reward, but also when their performance was more rather than less efficacious. To examine the time course of control evaluation and motivation, we separately analyzed two event-related potentials (ERPs): (1) the P3b, an index of motivational value occurring soon after the incentive cues are presented; and (2) the contingent negative variation (CNV), an index of preparatory cognitive effort/attention peaking immediately prior to the presentation of the Stroop stimulus. Consistent with our prediction that reward and efficacy should influence early stages of control evaluation,

we found that both of these led to increases in the post-cue P3b. Furthermore, consistent with our prediction that these two incentive components should subsequently influence the mobilization of cognitive effort, we found that reward and efficacy also increased the amplitude of the CNV. Increases in P3b and CNV in turn independently predicted improved performance on a given trial. Thus, participants allocated more control when it was more efficacious and when it was more rewarding, resulting in improved performance. Our findings confirm predictions of the EVC model, and highlight the important role efficacy plays in determining when and how individuals invest their cognitive effort.

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Nanosymposium

362. Data Analysis: Neuronal Networks

Location: Room S402

Time: Monday, October 21, 2019, 1:00 PM - 2:30 PM

Presentation Number: 362.01

Topic: I.07. Data Analysis and Statistics

Support: NSF NCS-FO: 1835268/1834994
NSF STC award CCF-1231216

Title: How anti-learning affects chance levels of population decoding accuracy

Authors: *E. M. MEYERS;
Hampshire Col., Amherst, MA

Abstract: Population decoding methods have become a popular way to analyze data from a range of neural recording modalities, including single unit recordings, EEG/MEG signals, and fMRI activity. In these analyses, a pattern classifier predicts which experimental conditions are present, based on recorded neural activity (Meyers and Kreiman, 2011). To assess whether information is in a neural signal, the prediction accuracy is compared to what would be expected by chance if the classifier was merely guessing. While methods have been developed to assess when these decoding accuracies are statistically significant (Combrisson and Jerbi, 2015), these methods do not account for the fact that when cross-validation is used, there are statistical dependencies between the training and test sets. These dependencies can lead to a phenomenon called 'anti-learning' (Kowalczyk and Chapelle, 2005) where the classification accuracy appears to be below chance during baseline periods when there should be no information present (e.g., a 20% classification accuracy when chance is 50%), which has lead researchers to question whether there is a mistake in their analyses. Here, we explain why this anti-learning phenomenon occurs, and give a method that can accurately assess when decoding accuracies are statistically significant. This method can be used to infer when information is first present in a brain region,

which can be useful for tracking information flow through the brain in order to understand the neural algorithms that underlie complex behaviors.

Disclosures: E.M. Meyers: None.

Nanosymposium

362. Data Analysis: Neuronal Networks

Location: Room S402

Time: Monday, October 21, 2019, 1:00 PM - 2:30 PM

Presentation Number: 362.02

Topic: I.07. Data Analysis and Statistics

Support: NIH grant R01NS089679
NIH grant R01NS104925
NIH grant R24NS098536
NVIDIA Investigator grant to Sober lab
NVIDIA Investigator grant to Gardener lab

Title: Vak: An open-source software library for high-throughput, automated segmentation and annotation of vocalizations with neural networks

Authors: *D. A. NICHOLSON[1], Y. COHEN[2];
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Abstract: More and more frequently, neuroscientists are acquiring petabyte-scale datasets of neural activity and behavior, including vocal behavior such as speech, birdsong, and ultrasonic rodent calls. However, annotating animal vocalizations remains a time-consuming task. This analysis bottleneck hinders scientists as they investigate how the brain learns and produces vocalizations.
To address this bottleneck, we present vak: https://github.com/NickleDave/vak. This software library enables researchers to use neural networks to automate the process of segmenting and annotating animal vocalizations. vak provides a convenient interface so that users convert audio files or spectrograms they have generated, along with annotations, into datasets used to train neural networks. Once trained, the neural networks can be applied to new data to find segments and predict their labels. Importantly, users can work with a wide variety of annotation formats, such as Praat textgrid files or Audacity label tracks, thanks to the tool crowsetta (https://crowsetta.readthedocs.io/en/latest/) built into the library. vak is completely free and open-source; essentially it is a lightweight wrapper around well-tested and actively maintained Python libraries such as Tensorflow and numpy.
As a demonstration, we show how we used vak to train TweetyNet, a neural network architecture (https://github.com/yardencsGitHub/tweetynet). We find that, compared to other approaches, TweetyNet achieves higher segmentation accuracy and lower syllable error rate (a distance

metric that accounts for mis-labeled segments) with less training data than other approaches using a publicly shared dataset of Bengalese finch song (https://figshare.com/articles/BirdsongRecognition/3470165). We then show that with TweetyNet models we can accurately label days of song from another dataset of Bengalese finch song (https://figshare.com/articles/Bengalese_Finch_song_repository/4805749) as well as hundreds of hours of complex canary song. To further demonstrate utility for neuroscientists, we also apply TweetyNet to other publicly available datasets of animal vocalizations, including egyptian bat vocalizations (https://www.nature.com/articles/sdata2017143) and human speech (https://www.kaggle.com/nltkdata/timitcorpus/home).Our goal is to present vak as a tool that will empower and democratize scientists studying vocalizations, just as open-source, community-developed tools have revolutionized disparate fields like neuroimaging, bioinformatics, and astrophysics. We look forward to receiving feedback from the neuroscience community.

Disclosures: D.A. Nicholson: None. **Y. Cohen:** None.

Nanosymposium

362. Data Analysis: Neuronal Networks

Location: Room S402

Time: Monday, October 21, 2019, 1:00 PM - 2:30 PM

Presentation Number: 362.03

Topic: I.07. Data Analysis and Statistics

Support: NSFC General Program 61876032

Title: Multi-object optimization on structural and functional community structures

Authors: *S. GU, K. LI;
Univ. of Electro. Sci. and Technol. of China, Chengdu, China

Abstract: Modular brain networks are important tools to understand brain structure, function, and development. A lot of investigations have been done on structural networks constructed on neural fibers from diffusion data and functional networks defined as statistical associations of time series. Yet there is rare work discussing how these modular structures are related to each other. Or more specially, what kind of transitions happen when the modular structure shifted between the structure and functional ones? In the current research, we propose a novel framework that utilizes the multi-object optimization tools to investigate the cross-modality community structure of structural and functional networks. First, we develop the co-optimize algorithm and find that the cross-modality shift of community structure happens in a stepwise rather than continuous pattern where the normalized mutual information of neighboring community structures changes dramatically at the transition point. Next, we define the cross-modality flexibility of a node as its frequency of changing community association along the

Pareto-frontier and cross-modality modular capacity as the area below the Pareto-frontier. Compared to the single-modality analysis of community structure, the cross-modality methods proposed in the current work pays more attention to how a subject's brain networks in different modality are related with each other thus potentially can be applied on the individual level analysis.

Disclosures: **S. Gu:** None. **K. Li:** None.

Nanosymposium

362. Data Analysis: Neuronal Networks

Location: Room S402

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Presentation Number: 362.04

Topic: I.07. Data Analysis and Statistics

Support: NSF Career Award IIS-1254123
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Ideas Lab IOS-1556388
Rose Hill Foundation

Title: Quantifying information transmitted by large neural populations

Authors: J. BERKOWITZ[1], ***T. O. SHARPEE**[2];
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Abstract: Recent technological advances make it possible to simultaneously measure responses of unprecedented numbers of neurons. However quantifying and characterizing responses of these large neural populations remains a challenge. Mutual information provides a rigorous way to quantify which sensory or motor variables are encoded in a neural population. However, evaluation of the mutual information is known to be generally intractable for large systems due to the exponential growth in the number of terms that need to be evaluated. Here we show how information contained in the responses of large neural populations can be effectively computed provided the input-output functions of individual neurons can be measured and approximated by a logistic function applied to a potentially nonlinear function of the stimulus. Neural responses in this model can remain sensitive to multiple stimulus components.We show that the mutual information in this model can be effectively approximated as a sum of lower-dimensional conditional mutual information terms. The approximations become exact in the limit of large neural populations and for certain conditions on the distribution of receptive fields across the neural population. We empirically find that these approximations continue to work well even when the conditions on the receptive field distributions are not fulfilled. The computing cost for the proposed methods grows linearly in the dimension of the input and compares favorably with other approximations.

Disclosures: **J. Berkowitz:** None. **T.O. Sharpee:** None.

Nanosymposium

362. Data Analysis: Neuronal Networks

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Topic: I.07. Data Analysis and Statistics

Support: NSF grant ECCS-1631820
NIH grant MH112180
NIH grant MH108148
NIH grant MH103222

Title: Temporal neural connectivity dynamics with TMS-EEG in schizophrenia

Authors: *D. GUPTA[1], X. DU[2], E. HONG[3], F.-S. CHOA[4];
[1]Univ. of Maryland Baltimore County, Baltimore, MD; [2]Maryland Psychiatric Res. Ctr., Catonsville, MD; [3]Maryland Psychiatric Res. Ctr., Baltimore, MD; [4]UMBC, Baltimore, MD

Abstract: Transcranial magnetic stimulation (TMS) has gained popularity for treatment of schizophrenia, depression, migraine and even post-traumatic stress disorder. Although patients report positive feedback after TMS treatments, the underlying brain mechanisms such treatments are still unknown. Here, we study temporal connectivity dynamics by analyzing electroencephalography (EEG) response to TMS subthreshold pulse administered at the left motor cortex from schizophrenia patients and healthy controls (11 channels @ 1000Hz). EEG has the highest temporal resolution and hence, together with TMS, can be the best full brain neuroimaging modality for investigating global causality. In our experiments, each trial was 4 seconds apart. We chose epoch size as 1000ms post 50ms of the TMS pulse to study dynamic connectivity and to avoid the TMS-induced noise. We then apply a finite impulse response bandpass filter of 1 to 50Hz. Next, peak to peak threshold value of 100μV was filtered in a sliding window technique with a window size of 200ms and 50ms shift in MATLAB based EEGLAB and ERPLAB toolbox for detecting noisy epochs. These noisy epochs with artifacts were discarded before averaging all epochs for calculating event related potential (ERP). We then computed connectivity between each channel pair by applying sliding window on ERP with a window size of 200ms and 20ms shift. This resulted in connectivity metric for 55 channel pairs over 41 time windows. After statistical analysis, we found that for controls, steady connectivity exists between frontal and temporal regions of the brain, whereas for patients the frontal was steadily connected with the parietal regions. In summary, our findings from statistical analysis of sliding window approach shows that dynamic neural pathways in schizophrenia differ from that of healthy controls if left motor cortical regions are stimulated with TMS subthreshold pulse at high temporal resolution. We will further apply this approach for TMS to be administered to

other brain regions for exploring neural pathways, building causal maps, understanding plasticity and developing therapeutic treatments.

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Nanosymposium

362. Data Analysis: Neuronal Networks

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PRICE-CTSI-IOA ARG DTD 03-26-2008
Department of Psychology at University of Florida
McKnight Brain Research Foundation
Center for Cognitive Aging and Memory

Title: Chronic intranasal oxytocin administration in older men enhances right TPJ functional MRI connectivity during social perception

Authors: *P. A. VALDES-HERNANDEZ[1], M. HORTA[1], I. FRAZIER[1], E. PORGES[1], R. POLK[1], E. PEREZ[1], M. OJEDA[1], Y. CRUZ-ALMEIDA[1], J. P. MORRIS[2], D. FEIFEL[3], N. EBNER[1];
[1]Univ. of Florida, Gainesville, FL; [2]Univ. of Virginia, Charlottesville, VA; [3]Univ. of California, San Diego, CA

Abstract: Growing evidence suggests a modulatory role of acute intranasal oxytocin (OT) on fMRI connectivity (FC). However, only one study applied chronic OT and found increased FC between anterior cingulate and dorsomedial prefrontal cortices at rest in younger adults. Currently nothing is known about chronic OT effects on FC in the aging brain. We determined the effects of chronic OT on whole-brain FC in older men (&gt55 years) who were randomly assigned to a 4-week intranasal self-administration of either 48 IU/day of OT (14 participants) or placebo (P; 13 participants). Pre- and post-intervention fMRIs were acquired on a 3T Philips Achieva during the Heider-Simmel Task, in which participants passively watched moving shapes that either elicited the impression of goal-directed interactions (social) or appeared to randomly move (non-social). Whole-brain Region-of-Interest (ROI)-to-ROI FC were estimated. For each condition/visit, the effect ($\beta_{condVISIT}$) of treatment (OT, P) on each connection was estimated using GLM, controlling for age, cognitive status and image quality. The T-contrast $\beta_{socPOST}$-$\beta_{nonsocPOST}$-β_{socPRE}+$\beta_{nonsocPRE}$ was tested. For each ROI seed, the contrast was Bonferroni

thresholded across ROI targets. Network-based-analysis (FWE *p*&lt0.05) yielded a subnetwork of significant size/mass. Chronic OT increased FC during social vs. non-social conditions between lateral occipital cortices, right I, II and VII and IX crura of the cerebellum, right inferior frontal gyrus (IFG-R), right planum temporale (PT-R), the cluster containing the right superior/middle temporal, supramarginal and angular gyri (C_ROI-R), and its left counterpart. C_ROI-R was the ROI with the most connections, suggesting its central role in the network. No significance was reached with $t=\beta_{socPRE}-\beta_{nonsocPRE}$, supporting the need to account for inter-individual variability at pre-intervention. The center of C_ROI-R coincided with the temporoparietal junction (TPJ-R), a structure known to be involved in visual attention to social cues. In addition, TPJ-L is involved in the perception of mental states of others. The detected crura is involved in working memory and processing of emotional, social, and language tasks, which might explain the recruitment of regions belonging to the "language network": IFG-R, PT-R and both TPJs. Our findings suggest that chronic OT enhances a cortico-cerebellar network mainly dedicated to visual, language, and socioemotional processing in older men during social perception, providing first evidence of chronic OT's impact on the aging social brain.

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Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

Location: Room N427

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 444.01

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant EY024984
BrightFocus G201027
Indiana Department of Health 15779
Indiana Department of Health 26343

Title: Human pluripotent stem cell-derived retinal ganglion cells display extensive neurite outgrowth with target recognition

Authors: *C. M. FLIGOR[1], P. K. SHIELDS[1], K. B. VANDERWALL[1], J. S. MEYER[2]; [1]Biol., IUPUI, Indianapolis, IN; [2]Indiana Univ., Indianapolis, IN

Abstract: Numerous degenerative disorders adversely affect retinal ganglion cells (RGCs), with injury to their axons resulting in vision loss or blindness. However, there has been a lack of success in the development of replacement strategies for RGCs due to obstacles such as the long distance outgrowth of RGC axons and the formation of functional synapses with post-synaptic

targets. The current study establishes human pluripotent stem cells (hPSCs) as a reliable tool to test the ability of RGCs to project long-distance neurites and display target recognition with appropriate brain regions. Retinal organoids were generated following established protocols from CRISPR-engineered hPSCs which allowed for the identification of RGCs via a fluorescent reporter. As the primary post-synaptic target of RGCs, the lateral geniculate nucleus (LGN) was extracted from P0-P3 mice and plated for co-culture with hPSC-derived RGCs. After one week, samples were analyzed for the extent of RGC outgrowth, including neurite length, number and directionality of outgrowth. Additionally, samples were collected for protein analysis via western blot or ICC. While hPSC-derived RGCs were found to express synaptic proteins in culture, this expression was significantly enhanced in the presence of LGN explants. The average neurite length of RGCs co-cultured with LGN explants was significantly increased compared to control RGCs cultured alone or with explants of olfactory bulb (OFB). Sholl analysis indicated RGCs co-cultured with LGN displayed significantly more neurites extending from RGC aggregates and more neurites in close proximity to explants compared to OFB control. Additionally, RGCs displayed recognition of appropriate targets as neurites closer to the LGN were significantly longer compared to neurites in the same location of OFB co-cultures. While hPSC-derived RGCs provide an unlimited source for cell replacement strategies, a number of obstacles remain, particularly the long distance extension of neurites and formation of synaptic contacts. Results of this study demonstrate that the *in vivo* environment likely modulates RGC neurite outgrowth. As such, these results will facilitate the eventual use of hPSC-derived RGCs for cell replacement, *in vitro* disease modeling and pharmaceutical screening.

Disclosures: C.M. Fligor: None. **P.K. Shields:** None. **K.B. VanderWall:** None. **J.S. Meyer:** None.

Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

Location: Room N427

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 444.02

Topic: A.03. Stem Cells and Reprogramming

Support: ISCRM training grant
Paul G. Allen Family Foundation brain grant 11856
NEI EY021482

Title: Single cell RNAseq analysis of human fetal retina and retinal organoids

Authors: *A. SRIDHAR[1], A. HOSHINO[1], L. DAI[1], A. K. HAUGHAN[1], A. CHITAZAN[2], K. M. ESCHENBACHER[1], I. A. GLASS[3], T. A. REH[1];
[1]Dept. of Biol. Structure, [2]Dept. of Biochem., [3]Pediatrics, Univ. of Washington, Seattle, WA

Abstract: Human stem-cell derived retinal organoids represent a highly accessible and amenable system for studies of retinal development and disease. They can accurately mirror early stages of human retinogenesis in a stepwise, temporal sequence, and the organization and expression of major classes of retinal neurons is recapitulated. Organoids have been especially successful in facilitating the differentiation and maturation of photoreceptors, which acquire the initial stages of outer segment morphology and phototransduction protein-expression in long-term 3D cultures. However, development and maturation of inner layer retinal neurons such as bipolar and ganglion cells are limited in organoids. Additionally, it is not clear if organoids can reproduce the cellular composition, diversity and genesis of the human fetal retina, as direct comparisons of organoids with the fetal retina have been limited. This is particularly relevant, since the human retina develops along a large spatial-temporal gradient, where the central retina is accelerated by several weeks compared to the periphery, and it is not known if retinogenesis in organoids recapitulates the developmental axis of the retina. Therefore, we used single cell RNAseq (10x Genomics) analysis, Immunostaining and RNA seq analysis to compare organoids to analogous stages of the fetal retina. Our results demonstrate for the first time that organoids follow similar pseudotime retinal lineages as the fetal retina, but differ in their cellular composition and maintenance of inner retinal organization at later stages. To test if this lack of organization in organoids is due to culture conditions, we compared the morphology and single cell RNAseq data of organoids with fetal retina tissue maintained *in vitro.* Our analyses show that inner retinal cell types, such as bipolar cells, amacrine and horizontal cells develop well in cultured fetal retina but not in organoids, indicating that culture conditions alone do not account for the deficiencies seen in retinal organoids. Overall, these experiments represent the first direct single cell analysis comparisons of organoids to fetal tissue, and will help to identify strategies to better facilitate organoids for translational studies of the retina.

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Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

Location: Room N427

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 444.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIRM GC1R-06673-A: CRP

Title: Using organoid models to study human cortical development

Authors: *M. ANDREWS[1], A. BHADURI[2], A. R. KRIEGSTEIN[3];
[1]Univ. of California, San Francisco (UCSF), San Francisco, CA; [3]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., [2]Univ. of California San Francisco, San Francisco, CA

Abstract: The cerebral cortex is vital for all cognitive function and is expanded in humans compared to other species. Abnormal cortical development often leads to cortical malformation and is a leading cause of epilepsy and developmental delay. Due to significant differences in cortical size and composition between humans and rodents, there is need for human-specific models to study normal development and disease consequences. Brain organoids, self-organizing three-dimensional models that recapitulate aspects of human brain development, can be made from pluripotent stem cells and maintained in culture for many months. Recent studies have begun to utilize organoids to model interactions between brain regions, circuit formation, and neurodevelopmental disease. However, the extent to which developmental processes are accurately represented in organoids is currently unclear, and reported limitations regarding structural organization, cellular health, and the stability of the cultures over time have demonstrated the need for a thorough comparison between organoids and primary cells. We have performed a direct comparison of cortical organoids and primary human cortical samples throughout neurogenesis using single cell RNA sequencing and complementary immunohistochemical analyses. Pluripotent stem cells driven toward neural induction and then patterned into dorsal telencephalon have a remarkable ability to make neural cells that proliferate, divide and differentiate into the appropriate broad classes of cells found in developing human cortex. However, the specificity of cellular subtype is not as clearly resolved in organoids as during normal development. This lack of specificity in cellular identity is problematic for maturation of these cells, and pseudoage analysis reveals substantial dysregulation of primary progenitor maturation programs in organoids. Moreover, differentially expressed genes enriched in organoids highlight pathways reflective of metabolic and ER stress. Although organoids are a powerful model system, a better definition of their limitations and the best utilization of these models is required as we strive to both improve our understanding of the brain and how best to study it.

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Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

Location: Room N427

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 444.04

Topic: A.03. Stem Cells and Reprogramming

Title: Vascularization of cerebral organoids by incorporation of endothelial cells

Authors: *J. LEASURE[1], L. WANG[1], A. JAMBUSARIA[1], S. G. ONG[2], J. REHMAN[3]; [1]Dept. of Pharmacol., [2]Pharmacology, Med., [3]Medicine, Pharmacology, Bioengineering, Univ. of Illinois Chicago, Chicago, IL

Abstract: Introduction: Cerebral organoids derived from pluripotent stem cells are emerging as an important platform to investigate neuronal mechanisms and disease. Traditional approaches to generate cerebral organoids rely on differentiating induced pluripotent stem cells (iPSCs) into neuroectodermal progenitor lineages and allowing these cells to mature into neurons and glial cells in a 3D-matrigel environment. However, most current cerebral organoid models lack a vasculature. Inclusion of vascular endothelial cells could allow for the study of cross-talk between neuronal cells and endothelial cells, as well as possibly model the blood-brain barrier in health and disease.
Methods: In order to incorporate endothelial cells (ECs) into cerebral organoids, we first generated human iPSC-derived embryoid bodies and neuroectoderm by providing neural differentiation cues. On day 10 of differentiation, the cells were embedded into Matrigel, with and without addition of human brain ECs (D3 line) and also in the presence or absence of the endothelial growth factor VEGF to ensure endothelial cell growth. At day 25, organoids were collected for paraffin embedding, immunohistochemistry and qPCR analysis.
Results: The assessment of the post-mitotic neuronal marker TuJ1 by immunohistochemistry demonstrated a significant decrease in neuronal differentiation following the incorporation of ECs into cerebral organoids. We evaluated expression of the neural progenitor marker Nestin by qPCR and also found a decrease in Nestin mRNA in the organoid. We also found that VEGF was essential to ensure survival of ECs. We also found that ECs formed vessel-like structures.
Conclusions: Our data suggests that brain ECs can be incorporated into cerebral organoids and form vascular-like structures. Such an orgaoind may be well-suited to study the blood-brain barrier homeostasis and pathogenic mechanisms of the the blood brain barrier in iPSC-derived human cerebral organoids. However, incorporation of ECs or the addition of VEGF necessary for EC survival may affect neuronal differentiation. Further mechanistic studies using this novel vascularized cerebral organoid model will help us study the interactions between neural lineage cells and endothelial cells.

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Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

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Presentation Number: 444.05

Topic: A.03. Stem Cells and Reprogramming

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Burroughs Wellcome Fund 1018707
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NIMH U01MH115727

Title: Accelerated production of human stem cell-derived neural progenitor cells for large-scale genetic screens and multiplexed transcriptomic analysis

Authors: *M. F. WELLS[1,3], M. R. SALICK[4], F. PICCIONI[2], E. J. HILL[3], J. M. MITCHELL[3,1], J. NEMESH[1], S. GHOSH[1], D. MEYER[1], C. MELLO[1], K. RAGHUNATHAN[1], D. HO[4], O. PIETILAINEN[1,3], R. NEHME[3,1], A. KAYKAS[5], S. MCCARROLL[6,1], K. EGGAN[3,1]; [1]Stanley Ctr. for Psychiatric Res., [2]Broad Inst., Cambridge, MA; [3]Stem Cell & Regenerative Biol., Harvard Univ., Cambridge, MA; [4]Neurosci., Novartis Inst. For Biomed. Res., Boston, MA; [5]Neurosci., Novartis Institutes for Biomed. Res., Boston, MA; [6]Dept. of Genet., Harvard Med. Sch., Boston, MA

Abstract: Samples of human brain tissue are rare and difficult to manipulate experimentally. As such, accurate models of human neural cells are needed to conduct scalable and high-throughput investigations of the molecular mechanisms that govern normal and diseased cellular phenotypes. Here, we describe our progress towards generating and employing *in vitro* stem cell-derived models of the human neural progenitor cells (NPCs), which play a vital role in early brain development by acting as an intermediate proliferative cell type in the pathway from pluripotent stem cells to fully functional neurons and glia. NPC dysfunction has been linked to several neurodevelopmental disorders, including schizophrenia, autism, and Zika (ZIKV) Congenital Syndrome. Typical *in vitro* stem cell-derived NPC model systems usually take anywhere from 14-50 days to generate using conventional methods. We recently created human Stem cell-derived Ngn2-accelerated Progenitor cells (SNaPs), which are produced using a novel 48 hour induction protocol. Large quantities of highly pure SNaPs that express several canonical transcript and protein markers of human NPCs can be manufactured in a fraction of the time required for standard techniques. SNaPs are proliferative, multipotent, and able to self-aggregate into neurospheres under low attachment conditions. Importantly, SNaPs are susceptible to ZIKV infection and viral-mediated cell death, while also being able to support active replication of this virus. Given the efficiency of the SNaP system, we were able to perform a first-of-its-kind whole genome CRISPR-Cas9 positive-selection survival screen that detected hundreds of host factors for the virus, as well as genetic drivers of proliferation. In addition, the ability to reproduce this method in 48 stem cell lines allowed us to conduct “village-in-a-dish” experiments in which human stem cell lines from dozens of different donors were maintained as pooled cultures in single flasks prior to genomic and/or transcriptomic analyses. This mixed-culture approach revealed inherent growth differences among SNaP lines, and located expression quantitative trait loci (eQTLs) that are relevant to ZIKV infectivity. Together, our findings support the use of SNaPs for 2-D and 3-D modeling of human neurodevelopment in culture.

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Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

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Presentation Number: 444.06

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Common Fund

Title: Controlled astrogliogenesis enables automated, high-throughput generation of astrocytes from human pluripotent stem cells

Authors: *V. M. JOVANOVIC, C. MALLEY, C. A. TRISTAN, P. ORMANOGLU, A. SIMEONOV, C. P. AUSTIN, I. SINGEC;
Natl. Ctr. For Advancing Translational Sci., NIH, Rockville, MD

Abstract: Astrocytes play important roles in normal brain development, synaptic function, neurodegenerative diseases, and various pathological conditions (e.g. opioid addiction). Derivation of human astrocytes from a scalable source such as induced pluripotent stem cells (iPSCs) is an attractive approach for disease modeling and drug discovery; however, currently available protocols are variable, inefficient, and lengthy (lasting up to several months). Here, we developed a highly efficient and controlled astrocyte differentiation protocol that overcomes the limitations of previously published methods. By identifying and simultaneously manipulating several critical pathways, we directly induced astrogliogenesis from iPSCs with over 90% efficiency in less than 30 days. These cells displayed astrocyte morphologies and expressed typical markers such as GFAP, NF-IA and S100-B. Unlike previous protocols, our approach enabled the direct transition of pluripotent cells into PAX6+ neuroepithelia and then into BLBP+ radial glial cells in only 7 days. By day 14, radial glial cells differentiated into S100B+ astroglia, thereby largely bypassing neurogenesis, followed by NF-IA expression at day 21 as demonstrated by immunocytochemistry and time-course RNA-Seq experiments. Single-cell analysis and comparison of iPSC-derived neuroepithelia to astrocytes confirmed strong enrichment of astroglial genes and absence of genes indicative of other cell types (e.g. neurons, oligodendrocytes, microglia, endothelial cells, pluripotent cells). Importantly, iPSC-derived astrocytes were functional and capable of taking up the neurotransmitter glutamate, storing glycogen intracellularly, and promoting neuronal survival and synaptic activity when co-cultured with neurons. Finally, the differentiation protocol was automated using a robotic cell culture system, which now enables standardized production of large quantities of astrocytes for high-throughput screening and other translational applications.

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Nanosymposium

444. Directing Pluripotent Stem Cell Differentiation

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Presentation Number: 444.07

Topic: A.03. Stem Cells and Reprogramming

Support: The Health Research Council of New Zealand
The Neurological Foundation of New Zealand
The University of Auckland
The Brain Research New Zealand Centre of Research Excellence

Title: Modelling the neurodegenerative disorder Huntington's disease by direct cellular reprogramming of adult human fibroblasts

Authors: *R. L. MONK, B. J. CONNOR;
The Univ. of Auckland, Auckland, New Zealand

Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterised by the progressive loss of GABAergic medium spiny neurons (MSNs) in the striatum. The study of neurodegenerative disorders such as HD has been impaired by limited access to live human disease-affected neurons. Cellular reprogramming of patient-derived somatic cells now offers an opportunity to generate live human neurons for the study of neurological conditions. We have developed a highly efficient protocol for direct reprogramming of adult human fibroblasts (HDFs) to induced neural precursor cells (iNPs) within 21 days by co-transfection of chemically-modified mRNA (cmRNA) encoding the pro-neural transcription factors *SOX2* and *PAX6* in a defined reprogramming medium. Directly reprogrammed iNPs express the neural transcription factors GSX2, ASCL1, DLX2, and MEIS2, required for the development of MSNs. We have optimised this protocol to generate high yields of DARPP32+ neurons within 30 – 45 days of differentiation using a combination of growth factors and small molecules in a BrainPhys^{TM} medium under physiological oxygen (5% O_2) conditions. HDFs from patients with HD (n=4; CAG repeat lengths 41 – 57) and normal subjects (n = 4; CAG repeat lengths 18 – 34) were directly reprogrammed with cmRNA *SOX2* and *PAX6*. The morphology of HD-derived neuronal cultures was compared to normal neuronal cultures at 30 and 45 days of differentiation. At both 30 and 45 days of differentiation HD-derived neuronal cultures demonstrated a significantly lower proportion of branched neurites per neuron compared to normal cultures. HD-derived neuronal cultures exhibited similar proportions of multipolar (≥ 2 neurites) and bipolar/unipolar (≤ 2 neurites) neurons, whereas normal neuronal cultures exhibited a significantly higher proportion of multipolar neurons than bipolar/unipolar neurons. By day 45 of differentiation the HD-derived neurons exhibited significantly smaller cell bodies and shorter neurites than normal neurons. These results demonstrate that HD-derived neurons exhibit a distinct alternation in neuronal morphology compared to normal neurons, providing a novel *in vitro* platform for studying the pathophysiology of HD.

Disclosures: **R.L. Monk:** None. **B.J. Connor:** A. Employment/Salary (full or part-time):; The University of Auckland. 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 University of Auckland. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); The University of Auckland.

Nanosymposium

445. Mechanisms of Epilepsy

Location: Room S403

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 445.01

Topic: B.10. Epilepsy

Support: Marie Skłodowska-Curie grant agreement no. 658418
MRC MR/L01095X/1
Epilepsy Research UK fellowship

Title: Modulating promoter activity to treat intractable epilepsy

Authors: Y. QIU[1], G. COLASANTE[2], C. DI BERARDINO[2], L. MASSIMINO[2], J. CORNFORD[1], A. SNOWBALL[1], S. JONES[1], S. GIANNELLI[2], M. WESTON[1], A. LIEB[1], S. SCHORGE[3], D. KULLMANN[1], V. BROCCOLI[2], ***G. LIGNANI**[1];
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Abstract: Epilepsy is one of the most important health burdens within the clinical neurosciences, and finding tools that open new mechanistic and therapeutic insights is a high priority. CRISPR is a powerful gene editing approach and it is now starting to be used to cure several pathologies. A variant of CRISPR, CRISPRa, allows to directly regulating the expression of endogenous genes by directly targeting their promoters (PromoTerapy), which allows expression of the full panoply of splice variants and untranslated regulatory sequences. In order to determine whether this strategy can be effective in genetic and non-genetic focal epilepsies, we applied CRISPRa technology to increase KNCA1 (encoding for Kv1.1) expression in excitatory pyramidal neurons in a mouse model of focal epilepsy. The overexpression of Kv1.1 leads to a decreased neuronal excitability, restoring physiological network activity. We have combined the functional analysis of neurons *in vitro* with the *in vivo* characterization of its translational potential through telemetry video-EEG and behaviour analysis. This approach is considered the proof of principle that PromoTerapy can be used to treat intractable focal epilepsies through the direct regulation of endogenous genes.

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Nanosymposium

445. Mechanisms of Epilepsy

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Presentation Number: 445.02

Topic: B.10. Epilepsy

Support: NHMRC Program Grant 10915693
NHMRC Project Grant 1143101

Title: Anticonvulsant properties of HCN4 channel block

Authors: *Q. KHAROUF[1], M. PHILLIPS[1], L. BLEAKLEY[1], E. MORRISROE[1], J. OYRER[1], A. LUDWIG[2], L. JIN[3], J. NICOLAZZO[3], E. CERBAI[4], N. ROMANELLI[4], S. PETROU[1], C. A. REID[1];
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Abstract: Epilepsy is a prevalent neurological disorder that affects a large proportion of people worldwide. Despite optimal treatment with modern antiepileptic drugs, about one third of patients will continue to have seizures, and side effects from these drugs are common. Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels are encoded by four genes (*HCN1-4*) and are considered good potential anticonvulsant targets due to their pacemaker properties. In this study we explore the impact of both pharmacological and molecular HCN4 channel 'block' on seizure susceptibility. EC18 (10mg/kg), a compound with a ~6-fold increased selectivity for HCN4 over HCN1 and HCN2 channels, reduced the seizure susceptibility of P21 C57/Bl6J wildtype mice in the subcutaneous pentylenetetrazole (s.c.PTZ) (100mg/kg, N=27) proconvulsant assay. EC18 also reduced PTZ-induced spike counts measured on EEG (N=6-7). In a battery of behavioural tests EC18 was shown to cause only a minor reduction in locomotion suggesting it was well tolerated (N=12). We also developed a tamoxifen-inducible conditional brain-specific HCN4 knock-out mouse model to test the impact of molecular knock-down on seizure susceptibility. Knockout of HCN4 in P57 adult mice reduced seizure susceptibility in the s.c.PTZ (100mg/kg, N=27) and kainic acid (30mg/kg,
N=14) proconvulsant tests with only a minor reduction in locomotion noted in behavioural analysis (N=47). Importantly, the anticonvulsant action of EC18 was blunted for the s.c.PTZ test in the HCN4 knockout mouse (N=10). Together these results suggest that HCN4 channels are

important mediators of neuronal network excitability and therefore are a good molecular target for anti-seizure drugs.

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Nanosymposium

445. Mechanisms of Epilepsy

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Topic: B.10. Epilepsy

Support: 5T32EB004314
2R01NS060757-05A1

Title: Low frequency corpus callosum stimulation suppresses cortical seizures more effectively than high frequency grey matter stimulation

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Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Previous work in an acute in vivo model of spontaneous seizures has shown that low frequency stimulation of the corpus callosum produced a seizure suppression rate of 95%. There are currently two FDA approved deep brain stimulation modalities available for patients with epilepsy focal high frequency (FHFS) and stimulation of the anterior nucleus of the thalamus (SANT). Both Neuropace and Medtronic devices rely on stimulation of a grey matter target using high frequency (>100 Hz) to abort seizures. To determine the relative efficacy of these stimulation methods we compared both approved techniques to the low frequency fiber tract stimulation paradigm in an in-vivo focal cortical seizure model acutely. 4 aminopyridine (4-AP) was injected in the primary somatosensory cortex of 28 rats (4 groups of 7) under anesthesia. For the three different stimulation groups local field potentials were recorded for one hour before stimulation as well as one hour during and following stimulation to determine the effect of stimulation on seizure duration. Stimulation was delivered in the corpus callosum low frequency (CCLFS) group as a 20 Hz bipolar pulse, whereas stimulation for FHFS and SANT was set to 200 Hz. Stimulation at 20 Hz of the corpus callosum produced a significant seizure suppression of 65% in the seizure focus and a 97% reduction in the mirror focus. However there was no observable effect of either FHFS or SANT on seizure duration or frequency. The fact that low frequency stimulation of the corpus callosum suppressed seizures by such a significant amount despite the severity of the model suggests that such a technique may prove more useful in treating refractory epilepsies than currently available DBS paradigms.

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Nanosymposium

445. Mechanisms of Epilepsy

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Presentation Number: 445.04

Topic: B.10. Epilepsy

Support: INCT-Translational Medicine
FAPESP
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FAEPA

Title: Cannabidiol prevents limbic and attenuates brainstem seizures, but do not modify anxiety-like behaviors, in a chronic protocol of epilepsy

Authors: *W. L. LOPES[1], R. A. DO VAL-DA SILVA[1], R. M. P. SILVA-JUNIOR[2], J. P. LEITE[1], N. GARCIA-CAIRASCO[2];
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Abstract: Epilepsies are neurological disorders characterized by the presence of epileptic seizures and neuropsychiatric comorbidities. The Wistar Audiogenic Rat (WAR) is a rodent strain capable of developing epileptic seizures in response to intense sound stimulation (audiogenic seizures, AS). Along the chronic protocol of AS (audiogenic kindling, AuK), the initially midbrain-dependent seizures, give rise to forebrain-dependent seizures through a process called limbic recruitment. Cannabidiol (CBD) is a compound present in the *Cannabis* and has been implicated in seizure and anxiety treatment. However, little is known about CBD effects in chronic protocols of epilepsy and in epilepsy-related comorbidities such as anxiety. The aim of this study was to verify if AuK could modify anxiety-like behaviors in WARs and verify the potential CBD anticonvulsant, antiepileptogenic and anxiolytic effects in a chronic protocol of epileptic seizures. WARs and Wistars (n=9-11/group; CEUA-FMRP: 057/2017) were submitted to AuK protocol (20 acoustic stimuli, twice a day). Animals were placed in an acrylic box and sound (120 dB) was applied for 1 minute, or until the development of tonic seizures. Animal behavior was analysed for 3 minutes: 1 before, 1 during, and 1 after the stimulus. CBD (25 mg/kg; i.p.) or vehicle treatment were initiated 24 h before the first stimulus and were maintained along the whole protocol (twice a day, 1 h before each stimulus). On the day after the 20th stimulus, CBD was administered 1 h before the open field (OF) and the light dark box (LDB) tests. On the next day, animals were submitted to a rebound stimulus (21st). Chronic CBD treatment attenuated brainstem seizures ($p<0,05$) and prevented the development of limbic seizures ($p<0,05$). No WAR with CBD treatment presented limbic seizures on 21st stimulus,

whereas they were present in 33% of the control WARs. Moreover, while AuK increased hippocampal CB1 receptors (CB1R) immunohistochemical staining in WARs, CBD treatment reduced it ($p<0,05$). AuK reduced the exploration in the center of the OF ($p<0,05$) and in the lit side of the LDB ($p<0,05$) in WARs, but it had no effect in Wistars. CBD did not modify anxiety-like behaviors in WARs. No Wistar presented any seizure, confirming the specific effect of acoustic stimuli in WARs. Our results showed that CBD attenuated brainstem seizures and prevented limbic recruitment, confirming its anticonvulsant activity and suggesting antiepileptogenic effects associated with a decrease in hippocampal CB1R staining. Anxiety-like behaviors were increased in WARs after the AuK, indicating that chronic seizures may increase anxiety, although CBD did not produce any anxiolytic effect.

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Nanosymposium

445. Mechanisms of Epilepsy

Location: Room S403

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 445.05

Topic: B.10. Epilepsy

Title: Interneurons derived from human pluripotent stem cells resemble primary human cortical interneurons *in vitro* and post-transplant in the rodent brain

Authors: *M. MASNAGHETTI, J. LEEDY, S. MEHRABANI, J. SPATAZZA, L. C. FUENTEALBA, S. LEE-SERTORIO, M. BERSHTEYN, H. NETHERCOTT, S. KRIKS, C. A. PRIEST, C. R. NICHOLAS;
Neurona Therapeut., South San Francisco, CA

Abstract: The circuitry of the brain maintains a delicate balance of neuronal inhibition and excitation. A hallmark of many neurological diseases is an imbalance of neuronal activity, often potentiated by dysfunction or depletion of inhibitory interneurons. Interneuron cell therapy has been proposed as a novel potential treatment option for diseases involving neural hyperexcitability such as chronic, drug-resistant epilepsy and neuropathic pain syndromes. It has been shown that mouse inhibitory interneuron precursor cells dissected from the medial ganglionic eminence (MGE) can disperse, integrate, mature, and provide increased functional inhibition following transplantation into postnatal rodent brain. Furthermore, mouse MGE transplants are efficacious in rodent models of multiple neurological disorders. To facilitate translation, a clinical-grade source of human interneurons is needed. Human pluripotent stem cell (hPSC) lines represent such a source. However, human interneurons derived in vitro from hPSC lines may not faithfully recapitulate MGE cortical-type interneuron ontogeny. Thus, we sought to characterize the molecular and functional fidelity of hPSC-derived interneurons to primary

interneurons from human fetal cortex. Using single-cell RNA sequencing and immunocytochemistry we found the hPSC-derived interneurons have a similar transcriptional profile to primary human fetal interneurons. When transplanted into immunocompromised mice and assessed for engraftment over a one-year time course, the hPSC-derived interneurons migrated and persisted in a similar fashion to the human fetal interneurons. Both hPSC- and fetal-derived cells appropriately differentiated into MGE cortical-type interneurons expressing specific markers such as LHX6, MAF, and GABA post-transplantation. Similar results were found when the hPSC-derived interneurons were transplanted into rodent disease models, demonstrating consistent migration, persistence, and fate. These results support further preclinical development of hPSC-derived interneurons toward potential first in-human clinical trials to treat diverse neurological disorders.

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Nanosymposium

445. Mechanisms of Epilepsy

Location: Room S403

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Presentation Number: 445.06

Topic: B.10. Epilepsy

Support: California Institute for Regenerative Medicine (CIRM DISC2-10525)

Title: Transplantation of human interneurons is effective in reducing focal and generalized seizures in two mouse models of temporal lobe epilepsy

Authors: *S. C. BROEER, M. B. PAREKH, L. C. FUENTEALBA, J. SPATAZZA, W. BLANKENBERGER, J. LEEDY, M. MASNAGHETTI, A. SPASOVA, H. NETHERCOTT, S. KRIKS, S. LEE, C. A. PRIEST, C. R. NICHOLAS;
Neurona Therapeutics, Inc, South San Francisco, CA

Abstract: More than one third of patients suffering from epilepsy do not achieve seizure freedom with modern antiepileptic drugs. One promising therapeutic strategy is the transplantation of inhibitory neurons to restore balance to the hyperexcitable epileptic neural network. We are developing a human medial ganglionic eminence-type GABAergic interneuron therapeutic derived from human embryonic stem cells (hESCs). At chronic time points post-transplantation, the hESC-derived interneurons disperse, mature, persist, integrate, and lead to long-term seizure suppression in two mouse models of temporal lobe epilepsy.
In both models, epilepsy is induced by prolonged status epilepticus (SE): either by an intrahippocampal injection of kainic acid (KA) or a systemic injection of pilocarpine (PILO). Mice develop chronic, recurrent, spontaneous electrographic (KA) or generalized (PILO) seizures a few weeks post-SE. In both models, animals received bilateral transplants of hESC-derived interneurons into the hippocampus or control injections of vehicle. Mice were monitored for seizures with hippocampal (KA) or cortical (PILO) electrodes at several time points for up to 10 months post-transplant (PT).
In the focal KA model, both groups had comparable electrographic seizure frequencies at one week PT. From 4 to 10 months PT, the group that received cell transplantation had 70-80% fewer electrographic seizures than the group that received vehicle, and the cumulative duration of seizures was reduced significantly. Similarly, in the PILO model, animals that received cell transplantation had about 50-65% reduction in generalized seizure frequency and duration from 6 to 10 months PT.
Transplanted human cells persisted in the epileptic mouse hippocampus for at least 10 months and expressed interneuron subtype markers. No ectopic human tissues or teratomas were found and no adverse events in animal behavior or health were observed.
In conclusion, hESC-derived interneuron transplantation reduced focal and generalized seizure burden in two models of temporal lobe epilepsy for 6-10 months PT, and the cells persisted and

distributed throughout the hippocampus, supporting the development of an inhibitory neuron cell therapy option for drug-resistant temporal lobe epilepsy.

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Nanosymposium

445. Mechanisms of Epilepsy

Location: Room S403

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 445.07

Topic: B.10. Epilepsy

Title: Comparative behavior study using two models of temporal lobe epilepsy in an immunodeficient mouse strain

Authors: W. BLANKENBERGER, S. C. BROEER, M. B. PAREKH, L. C. FUENTEALBA, J. SPATAZZA, J. LEEDY, M. MASNAGHETTI, C. ABILAY, C. R. NICHOLAS, *C. A. PRIEST;
Neurona Therapeutics, Inc, South San Francisco, CA

Abstract: Due to an increased interest in the development of biologicals such as monoclonal antibody, protein, gene and cell-based therapeutic agents for human neurological diseases, many groups are using immunodeficient mouse strains for preclinical testing. Currently, there is very little research on neuropharmacological behavioral testing using these immunodeficient mouse strains. We are developing a human stem cell-derived therapeutic for temporal lobe epilepsy (TLE), a common neurological disease that is associated with various behavioral comorbidities. To support this development, an in-depth behavioral characterization of the immunodeficient NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Sug}/JicTac (NOG) mouse strain was performed in two different chemoconvulsant-induced models of chronic TLE with an array of behavioral assays. We aim to determine the behavioral assays with the most consistent phenotype for each model in comparison to an age-matched group of naïve control NOG mice as a reference data set for future studies.
In both models, epilepsy was induced by prolonged status epilepticus (SE): either by an intrahippocampal injection of kainic acid (KA) or a systemic injection of pilocarpine (PILO). Mice developed chronic, recurrent, spontaneous electrographic focal (KA) or generalized (PILO) seizures a few weeks post-SE. Naïve control animals did not receive any treatment. All animals were individually housed and received nesting material. Behavioral testing was performed by 1-2 experimenters, who were blinded to the treatment of the mice. An open field test was conducted monthly starting one month post-SE to gather data on general locomotor activity and anxiety over an 8-month time course. Nest building, which reflects the animal's well-being and is sensitive to hippocampal damage, was assessed monthly. Hyperexcitability, novel object recognition, and novel placement tests were run twice, several months apart. These tests assess general health, fear responses, exploration, and memory. In addition, Y- and Barnes maze tests were run to assess spatial learning and memory. Lastly, a pentylenetetrazol test was performed to determine differences in seizure threshold.
Data from this study will be used to identify the behavioral tests that are most informative in preclinical testing when using NOG immunodeficient, epileptic mice.

Disclosures: W. Blankenberger: A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **S.C. Broeer:** A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock,

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Nanosymposium

445. Mechanisms of Epilepsy

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National Cheng Kung University Hospital, NCKUH-10602005
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NCKUH-10802012

Title: Transcranial direct current stimulation ameliorates status epilepticus in rats: From seizure severity, EEG, neuronal firing to epileptogenesis

Authors: *Y.-J. WU[1], C.-C. CHIANG[2], M.-E. CHIEN[1], C.-H. HUANG[1], K.-S. HSU[3], D. M. DURAND[4];
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Abstract: Status epilepticus (SE) is a state of prolonged and repeated seizures that can lead to permanent brain damage or life-threatening conditions. Transcranial direct current stimulation (tDCS) non-invasively provides a polarity-specific electric current to modulate brain excitability. Little is known about the therapeutic potential of tDCS in SE. Here, we aim to determine the tDCS effects on seizure severity, EEG and post-SE epileptogenesis in rats with kainic acid (KA)-induced SE. Rats were subjected to cathodal tDCS or sham stimulation over the dorsal hippocampus for 5 days. KA was intraperitoneally injected to induce SE. We used continuous video-EEG recording to monitor seizure activity, spike sorting algorithm to detect neuronal unit firing, immunostaining and Timm staining to evaluate neuron counts and mossy fiber sprouting, and ELISA for Brain-derived neurotrophic factor (BDNF) protein measurement. Two featured EEG patterns, high-frequency polyspikes and low-frequency spike-and-wave complexes, were identified in the hippocampal CA1 of KA-induced SE rats. tDCS elicited a significant decrease in severe seizures of Racine stages 4-5 in KA-induced SE rats. tDCS-treated rats manifested diminished high-frequency oscillation during SE, decreased chronic spontaneous spike activities and mossy fiber sproutings compared to sham. A decrease of hippocampal neuronal firing rate was also observed during and post-stimulation of cathodal tDCS. tDCS-treated rats also exhibited significantly lower hippocampal BDNF protein levels than sham immediately and 4 weeks after SE. A positive correlation between the hippocampal BDNF level and the seizure severity of SE was found. Our findings show that repeated cathodal tDCS can decrease seizure severity, alter ictal EEG pattern and reduce the chronic epileptogenesis in KA-induced SE rats, supporting the therapeutic potential of tDCS in severe prolonged seizures.
Keywords: Status epilepticus, Seizure, Electroencephalography (EEG), Mossy fiber sprouting, Brain-derived neurotrophic factor (BDNF), Transcranial direct current stimulation (tDCS)

Disclosures: Y. Wu: None. **C. Chiang:** None. **M. Chien:** None. **C. Huang:** None. **K. Hsu:** None. **D.M. Durand:** None.

Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

Location: Room S106

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 446.01

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

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Owens Family Foundation
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Title: Tau regulates neuronal mitochondrial DNA replication and its suppression by amyloid-β oligomers: Implications for Alzheimer's disease

Authors: A. NORAMBUENA, X. SUN, N. SHIVANGE, *G. S. BLOOM;
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Abstract: Mitochondrial dysfunction is associated with several neurological disorders, including Alzheimer's Disease (AD), but the underlying mechanisms remain poorly understood. We recently discovered nutrient-induced mitochondrial activity (NiMA), an inter-organelle signaling pathway whereby activation of the multi-subunit protein kinase, mTORC1, on lysosomes by insulin or amino acids (herein, nutrients) quickly stimulates mitochondrial oxidative metabolism (MitoOXPHOS) in cultured neurons and live mouse brain. Intriguingly, Tau was found to regulate mitochondrial DNA (mtDNA) replication through the NiMA pathway. Amyloid-β oligomers (AβOs), which activate mTORC1 at the plasma membrane, but not at lysosomes, by a Tau-dependent mechanism (Norambuena et al, 2017. *Alzheimers & Dementia* 13: 152-167), were found to counteract the effects of nutrients on both MitoOXPHOS and mtDNA replication (Norambuena, et al. 2018. *EMBO J* 37: e100241). These collective results prompted further investigation of the mechanism by which Tau regulates mtDNA replication and how such regulation may be compromised in AD. 5-ethyl-2´-deoxyuridine (EdU) incorporation in live neurons followed by copper click chemistry was used to image mtDNA replication in wild type (WT) and Tau knockout (KO) mouse cortical neuron cultures. Lysosomal mTORC1 activation involves its recruitment to the lysosome surface and detachment of its lysosome-associated inhibitor, the tuberous sclerosis complex (TSC). Mechanistically, we found that the TSC content on lysosomes not only is higher in Tau KO versus WT neurons, but is also relatively insensitive to nutrient stimulation. This process was rescued by re-expressing WT human Tau. Nutrients were found to suppress mtDNA replication in WT, but not Tau KO neurons, unless the latter expressed lentivirus-encoded wild type human Tau. Enhancing lysosomal mTORC1 levels in Tau KO neurons by downregulating TSC expression or forcing mTORC1 to lysosomes by overexpressing a fusion protein of the mTORC1 subunit, Raptor, fused to a lysosome-targeting signal restored nutrient-mediated suppression of mtDNA replication in Tau KO neurons. Lysosomal mTORC1 activity in neurons thus appears to be constitutively suppressed in the absence of Tau. Tau therefore enables nutrients to suppress mtDNA replication under non-pathological conditions, and is also required for the failure of nutrients to block mtDNA replication in the presence of AβOs. We propose that Tau is thereby part of nutrient-sensing machinery that functionally couples nutrient availability to mtDNA replication under normal conditions, and mechanistically links mitochondrial dysfunction to AD.

Disclosures: A. Norambuena: None. **X. Sun:** None. **N. Shivange:** None. **G.S. Bloom:** None.

Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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Title: Sex differences in tau pathological development in mouse models of AD

Authors: K. J. TU, A. WEI, A. J. LAU, L. CHEN, ***T. LI**;
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Abstract: Alzheimer’s disease (AD) is the most common cause of dementia. Accumulating evidences show that while men may have a greater risk for mild cognitive impairment (MCI), women are more likely to develop AD. Women make up almost two-thirds of AD patients in the United States. Despite substantial efforts in AD research over the decades, the biological role of sex in the neurodegenerative process has remained unclear. Recent studies suggested that women have greater longitudinal rates of cognitive and functional progression than men. To understand the disease mechanism of AD, we generated a mouse model (Tau4RΔK) that induced the pathological conversion of wild type tau, which spread in a prion mechanism to other regions of the brain, mimicking AD patients. We found that while the onset of tau pathology in both female and male Tau4RΔK mice started at the same time (around 6 months of age), female mice showed more abundant tau pathology at 16 months of age, suggesting tau may develop faster in female mice during aging, thus contributing to the AD sex difference. Since Tau4RΔK mice developed tau pathology and brain atrophy at a relatively young age, we were unable to determine whether the sex difference could be caused by the onset of tau pathology during aging. To solve this problem, we selected an independent mouse line (Tau4RΔKL) that expressed lower levels of mutant tau fragment. The Tau4RΔKL mice did not develop tau pathology until an older age (until 12 months of age). Using this new mouse model, we found that the onset of tau pathologies were similar in males and females; however, the tau pathology progressed much faster in female mice. Our two independent mouse models showed that the sex difference might not be related to the onset of tau pathology but related to the progression of tau pathology during aging. Our data indicated that the difference in tau pathological progression might be the reason behind the sex differences in AD. Aging and sex are two of the most important risk factors in AD. Our studies showed these two factors might play a synergistic role during AD development.

Our novel mouse model that mimics AD pathologies allowed us the opportunity to understand the mechanisms of sex differences in AD during aging.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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

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Title: Aggregated tau and RNA-binding proteins in Alzheimer's disease: Musashi1 and Musashi2 in nuclear dysfunction

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Abstract: RNA-Binding Proteins (RBPs) accumulate and aggregate in different neurodegenerative diseases, including Alzheimer’s disease (AD). The Musashi (MSI) family is a group of RBPs which includes two homologous proteins, Musashi1 and Musashi2 (MSI1 and MSI2). MSI proteins are known to be expressed in neuronal stem cells. However, there is no data reported on their functions in AD or other neurodegenerative diseases. Recent studies have shown that different RBPs, such as TDP-43, FUS, TIA-1 and many others, form toxic aggregates that interact with tau and potentially influence its toxicity in the neurons through alteration of stress granules (SGs). We previously demonstrated that MSI proteins form toxic aggregates *in vitro.* Additionally, we observed oligomeric MSI proteins in AD brain tissues, which also co-localized with tau oligomers. In the current study, we investigated the nuclear dysfunction mediated by tau/MSI complexes in a tau-inducible cell model (iHEK) and primary cortical neuronal cultures. Furthermore, we evaluated these changes in mouse and AD brain tissues. We performed High-resolution Microscopy and Atomic Force Microscopy to test whether human recombinant MSI contributes to the aggregation of toxic tau oligomers *in-vitro,* addressed the localization of MSI/tau complexes by Proximity Ligation Assay in ex-vivo AD brains, and

mouse models. Mass Spectrometric analyses have been performed with cytoplasmic/nuclear fractions and immunoprecipitated fractions from the cell lysates to evaluate how tau alters cell compartment distribution of different RBPs. We found that tau co-localized and accumulated with MSI in different cellular compartments in cells and AD brain, mainly in the nuclei of hippocampus and cortex. In the nuclei, tau oligomers form nuclear structures with MSI1 and MSI2, with specific orientation and shapes. Such aggregates effect nuclear membranes by impairing cellular localization of nuclear proteins, including several RBPs. Moreover, the formation of tau /MSI aggregates is coupled with a reduction of LaminA/C and LaminB1, perhaps by inducing nuclear lamina instability and changes in DNA condensation states. Our findings suggest that MSI proteins play a role in cellular dysfunction and AD pathogenesis, indicating tau aggregation and accumulation. Our data highlight a possible mechanism of neurodegeneration mediated by aggregated MSI proteins and tau oligomers in the nuclei of the cells, offering a promising opportunity to address new mechanistic insights.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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

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Title: Tau and TDP-43 synergize *in vivo* to promote neurotoxicity and neurodegeneration in a *C. elegans* model of Alzheimer's disease

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Abstract: Alzheimer’s disease (AD) is the most common neurodegenerative dementia disorder, affecting more than 24 million people worldwide. AD is defined by the presence of amyloid beta (Aβ) and tau aggregates in the brain, but up to 50% of patients also exhibit aggregates of the protein TDP-43 as a secondary pathology. Clinically, AD patients with secondary TDP-43 pathology have worse cognitive decline and a more rapid disease course. TDP-43 is already implicated in neurodegenerative disease as the major pathological protein aggregate in

amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP), two other devastating neurodegenerative diseases. Mutations in the gene coding for TDP-43 cause some cases of familial-inherited ALS, demonstrating that TDP-43 dysfunction is sufficient to cause disease. In patients with mixed Aβ, tau and TDP-43 pathology, TDP-43 dysfunction may synergize with neurodegenerative processes in AD, worsening disease. In a stringently selected autopsy cohort of individuals with advanced age and high burden of AD neuropathologic change, we have found that the presence of TDP-43 pathology is associated with more severe tau pathology and cognitive impairment, while the absence of TDP-43 pathology correlates with cognitive resilience. To test whether TDP-43 influences tau accumulation or neurotoxicity, we generated *C. elegans* expressing both wild-type human tau and TDP-43 pan-neuronally. We found that tau and TDP-43 synergize *in vivo* resulting in severely enhanced toxicity, movement dysfunction, and pathological protein accumulation. Characterizing the neurotoxic synergies between TDP-43 and tau in vivo is critical for understanding and treating mixed pathology AD.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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Presentation Number: 446.05

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

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Title: Pathological tau seeding and accumulation in a nonhuman primate model of Alzheimer’s disease

Authors: *D. BECKMAN[1], K. DONIS-COX[1], S. E. DEMOYA[2], S. OTT[1], W. G. JANSSEN[3], S. MULLER[4], J. H. KORDOWER[4], V. M. LEE[5], J. Q. TROJANOWSKI[5], J. MORRISON[1]; [1]California Natl. Primate Res. Ctr., UC Davis, Davis, CA; [2]Dept. of Pediatrics, Columbia Univ. Irving Med. Ctr., New York, NY; [3]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Dept Neurol Sci., Rush Univ. Med. Ctr., Chicago, IL; [5]Dept Pathol & Lab. Med., Univ. Pennsylvania Sch. Med., Philadelphia, PA

Abstract: There has been very little success in clinical trials for new candidate drugs for the treatment of Alzheimer’s disease (AD). Although rodent models are valuable for studying some aspects of AD pathogenesis, they do not recapitulate the full spectrum of the disease. The search for a more powerful translational model has led to the use of non-human primates (NHPs), phylogenetically closer to humans. The transition from age-related cognitive decline, which is

clearly evident in NHPs, to AD, is dependent on the death of specific subpopulations of pyramidal cells in association cortices that furnish long corticocortical projections. Currently, there are no data from the same cohort of NHPs linking end-stage neurofibrillary tangles (NFT), neuron death, and cognitive decline, hallmarks of AD pathology in humans. To explore a potential role of tau seeding in developing AD pathological progression in NHPs, we injected the entorhinal cortex (ERC, left hemisphere) and prefrontal cortex (right hemisphere) of 12 female rhesus monkeys (young and aged) with human AD tau fibrils or age-matched non-demented human brain extracts. Following a 6 month incubation period after tau fibril injection, preliminary analysis shows extensive neuroinflammation, with phospho-tau colocalizing with astrocytes and being surrounded by reactive microglia close to the injection site, followed by an increase in neuronal phospho-tau and NFT formation. Strong phospho-tau staining was observed also in the perirhinal cortex, hippocampus and contralateral ERC, suggesting tau propagation to adjacent areas and to the other hemisphere. Further analysis is necessary, but the preliminary data obtained so far shows the transport of tau aggregates along pathways connected to ERC, which is a critical hallmark in human AD pathology development. Through a comprehensive regional analysis, we are exploring the spatio/temporal sequence of tau aggregate transport and degeneration associated with the presence of NFTs in the monkey brain. In doing so, we hope to be able to temporally model the earliest phase of the degenerative cascade seen in AD and be able to compare it to synaptic alterations that occur in normal aging in NHPs.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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Title: Epigenetic age acceleration is associated with increased risk and distribution of tau pathology

Authors: *C. T. MCMILLAN[1], D. A. WOLK[2], F. B. JOHNSON[2], J. SCHNEIDER[3], D. BENNETT[3], P. L. DE JAGER[4], E. B. LEE[1];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Pennsyvlania, Philadelphia, PA; [3]Rush Univ., Chicago, IL; [4]Columbia Univ., New York, NY

Abstract: Age is perhaps the most well-established risk factor for neuropathological accumulation, including tau neurofibrillary tangles (NFTs) and amyloid plaques (Aβ), but is most often defined chronologically (e.g., years since birth). There is increasing evidence that individuals age at different rates and biological aging measurements (e.g., "Horvath's Clock") use a weighted summary of 353 CpG sites of DNA methylation (mDNA) to compute an individual's predicted, or "biological" age. We test the hypothesis that accelerated biological aging (mDNA age > chronological age) is a risk factor for increased NFTs and evaluate whether this is modified by presence of Aβ in Alzheimer's disease (AD) or absence of Aβ in primary age-related tauopathy (PART) who only develop NFTs.We computed mDNA age using Horvath's Clock algorithm and Illumina HumanMethylation 450 BeadChip data from dorsolateral prefrontal cortex tissue in autopsy-confirmed PART (N=119) and AD (N=223) individuals in the publicly-available Religious Orders Study and Memory & Aging Project (ROSMAP) cohort. Chronological age and mDNA age were positively correlated ($r=0.61$; $p<0.001$), consistent with previous assessments of several human tissue and cell types. We further defined "Age Discordance" as the linear regression residual between the prediction of chronological age from mDNA age, adjusting for sex: a lower discordance reflects delayed aging (mDNA age < chronological age) and a higher discordance reflects accelerated aging (mDNA age > chronological age). A Cox regression revealed that the probability of Braak Stage $\geq$III is associated with a main effect for Age Discordance in which accelerated aging individuals have increased risk for NFTs relative to delayed aging individuals (HR=3.5, CI=2.1-5.8, $p<0.001$). We did not observe an interaction between Age Discordance and Aβ-status (PART vs. AD; HR=1.1; CI=0.6-1.9; $p=0.76$) and only a relatively modest main effect for Aβ-status alone (HR=1.6; CI=1.1-2.4; $p=0.02$). Thus, mDNA alone may provide a strong mechanism behind risk for moderate or severe NFT pathological burden. Pairwise comparisons confirm this observation with a dose-dependent association between Age Discordance and NFTs: Braak Stage III/IV (M=0.13 years; SD=3.4) have higher age acceleration than Braak stage I/II (M=-1.39 years; SD=4.2) and Braak stage V/VI (M=0.63 years; SD= 3.2) have higher age acceleration relative to Braak stage I/II ($p=0.003$). Together, this evidence suggests that biological aging mechanisms, specifically mDNA, may provide a key source of risk for the accumulation of NFTs relatively independent of Aβ status.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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

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Title: Assay based on Tau-RD-GFP FRET pairs does not represent templated assembly of PHFs

Authors: S. KANIYAPPAN[1], K. TEPPER[1], J. BIERNAT[1], R. R. CHANDUPATLA[1], S. HÜBSCHMANN[1], S. IRSEN[2], S. BICHER[2], C. KLATT[2], E. M. MANDELKOW[1,2], ***E. MANDELKOW**[1,2];
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Abstract: Tau aggregation into amyloid fibers based on cross-beta structure is a hallmark of several tauopathies including Alzheimer Disease (AD). Trans-cellular propagation of Tau with pathological conformation has been suggested as a key disease mechanism. This is thought to cause the spreading of tau pathology in AD by templated conversion of naive tau in recipient cells into a pathological state, followed by assembly of pathological tau fibers, similar to the mechanism proposed for prion pathogenesis. In cell cultures the process is usually monitored by a FRET assay where the recipient cell expresses the Tau repeat domain (TauRD, with pro-aggregant mutation, e.g. ΔK280 or P301L, ~13.5 kD) fused to GFP-based FRET pairs (YFP or CFP, ~28 kD). Since the diameter of the reporter GFP (~4.8nm) is ~10 times larger than the β-strand distance (0.47nm) this points to a potential steric clash. Hence, we investigated the influence of GFP tagged (N-ter or C-ter) TauRD on their aggregation behavior in vitro. Using biophysical (light scattering), atomic force microscopy (AFM) and scanning-transmission electron microscopy (STEM), we found that the assembly of TauRD$^{\Delta K}$-GFP was severely inhibited, even in the presence of nucleation enhancers (heparin and/or pre-formed PHFs from TauRD$^{\Delta K}$ without GFP). Although some short fiber-like particles were observed they had a very different subunit packing, as judged by STEM. The mass per length (MPL) values of TauRD$^{\Delta K}$ fibrils are equivalent to 4.45 molecules/nm (see also Von Bergen et al., Biochem. 2006). This is very close to the theoretical value expected for a paired-helical fiber with 2 protofilaments and cross-β structure, confirmed by recent cryo-EM structures (Fitzpatrick et al., Nature 2017). By contrast, the elongated particles formed by TauRD$^{\Delta K}$-GFP have MPL values around 2.01, less than half of the values expected for PHFs, indicating that the subunit packing is distinct. Thus, both kinetic and structural observations are incompatible with a model whereby external Tau can form a template for PHF assembly of Tau-GFP in recipient cells. As a consequence, the observed

local increase of the FRET signal is likely explained by other processes which may even be independent of Tau (e.g. cytokine signalling, see Gorlovoy et al., FASEBJ 2009).

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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

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ERA-NET NEURON 32NE30_173678/1

Title: Brain regional calcifications link with tauopathy in P301L tau mice

Authors: R. NI[1], Y. ZARB[3], Z. KOVACS[2], G. KUHN[4], R. MÜLLER[4], Y. YUNDUNG[4], R. NITSCH[5], L. KULIC[5], A. KELLER[3], J. KLOHS[2];
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Abstract: Brain calcifications are observed in patients with neurodegenerative diseases, such as Alzheimer’s disease, Down syndrome and Frontal temporal lobe dementia. Recent study shows that calcification lead to oxidative stress in astrocyte and its neurotoxic marker expression. Here, we reported brain regional calcification in a P301L tauopathy mouse model of frontal temporal lobe dementia using multimodal high-resolution imaging. We assessed the P301L-tau transgenic mice at 3, 5, 9 and 18-25 months (n = 11 per group, both genders), for calcification by using *in vivo/ex vivo* high-field magnetic resonance imaging (MRI) using a gradient recalled echo sequence and micro-computer tomography (microCT). Immunohistochemical staining against glial fibrillary acidic protein, C3 subtype of astrocyte, CD31 (vessel marker), osteocalcin (calcification), AT8, AT100 (phosphorylated tau) and histopathology were performed. From the gradient recalled echo data phase maps and susceptibility weighted images (SWI) were computed. SWI and phase images as well as CT showed calcified deposits in the hippocampus, basal ganglia, cortex, thalamus and ossified cerebral vessels in P301L mice from 5 months-of-age, corroborated by osteocalcin staining of ossified vessel. The hippocampal calcification in P301L mice shown by SWI showed an increase with advancing age and tau pathology. In

conclusion, we describe regional calcification as a new phenotype of a murine model of tauopathy, which will serve as a model of the human disease conditions.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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

Support: NIH R56AG063344
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Title: A partial loss of function mutation of VCP is associated with vacuolar tauopathy

Authors: N. F. DARWICH[1], J. M. PHAN[1], E. SUH[1], M. GROSSMAN[1], L. MASSIMO[1], D. J. IRWIN[1], C. T. MCMILLAN[1], I. M. NASRALLAH[1], C. TORO[2], G. K. AGUIRRE[1], V. M. VAN DEERLIN[1], ***E. B. LEE**[1];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Adult NIH Undiagnosed Dis. Program (UDP) Natl. Human Genome Res. Inst., Bethesda, MD

Abstract: Valosin containing protein (VCP, also known as p97) is a AAA+ protein which hydrolyzes ATP in order to extract proteins from various cellular complexes. VCP mutations are known to increase ATPase activity leading to frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), motor neuron disease, Paget’s disease of bone and/or inclusion body myositis. Indeed, several genetic mutations have been linked to FTLD-TDP. In contrast, the only known genetic mutations that cause frontotemporal lobar degeneration with tau inclusions (FTLD-tau) involve *MAPT* which encodes the tau protein. We present a novel form of autosomal dominant FTLD-tau we have named Vacuolar Tauopathy (VT). Neuropathology at autopsy showed neurodegeneration in a frontal and temporal distribution with abnormal neuronal vacuoles and AD-like neurofibrillary tangles. In a remarkable instance of allelic heterogeneity, VT is associated with a novel mutation in *VCP*. Using recombinant protein, mutant VCP exhibited a significant 30% reduction in ATPase activity coupled with increased sensitivity to salt and heat inactivation *in vitro*. Moreover, treating human brain derived pathologic tau with VCP and the cofactor complex UFD1L-NPLOC4 resulted in reduced numbers of tau filaments by electron microscopy and decreased tau seeding activity in biosensor reporter cells. Finally, VCP mutation knock in mice were generated which exhibit enhanced tau protein accumulation

compared to wild type mice upon intracerebral microinjections of human brain derived pathologic tau. In summary, we describe a novel, partial loss of function VCP mutation associated with a novel autosomal dominant form of FTLD-tau. VCP appears to exhibit biochemical activity against tau filaments, reducing tau filaments, seeding and aggregation. VCP may represent a novel therapeutic target for the treatment of tauopathy.

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Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

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Title: Greater relative white matter burden is a distinct feature of tauopathies in frontotemporal degeneration spectrum

Authors: L. GIANNINI[1], S. XIE[2], D. A. WOLK[2], E. B. LEE[3], M. GROSSMAN[4], J. Q. TROJANOWSKI[5], *D. IRWIN[2];
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Abstract: Objective: To objectively quantify neuropathological white matter (WM) burden in relation to grey matter (GM) in frontotemporal lobar degeneration (FTLD) subtypes. Background: *Antemortem* distinction of FTLD proteinopathies, including tauopathies (FTLD-Tau) and TDP-43 proteinopathies (FTLD-TDP), is critical for disease-modifying therapies. Pathological heterogeneity in patterns of GM and WM pathology across FTLD subtypes is understudied. Shared neuropathological features of proteinopathies could facilitate *antemortem* diagnostic tools.

Design/Methods: We studied neuropathological burden in five cortical GM and adjacent WM regions in an autopsy cohort of FTLD (n=92) using a novel, validated digital image approach. Using linear mixed-effects models we examined absolute density of WM pathology and relative WM burden (i.e. WM-to-GM ratio) across FTLD subtypes (FTLD-TDP: type A/B/E=42 patients vs. type C=13; FTLD-Tau: progressive supranuclear palsy [PSP]=9, corticobasal degeneration [CBD]=11, Pick's disease [PiD]=11, *MAPT*-mutation carriers=6). Clinical diagnosis of behavioral-variant frontotemporal dementia (bvFTD) was in 42 FTLD-TDP and 23 FTLD-Tau. Clinical diagnosis of primary progressive aphasia (PPA) was in 13 FTLD-TDP and 14 FTLD-Tau.
Results: A positive linear association between absolute GM and WM burden was found in both FTLD-Tau ($p<0.001$) and FTLD-TDP ($p<0.001$). In FTLD-Tau, CBD had greater absolute WM burden than PSP ($p<0.001$) and PiD ($p<0.001$). In FTLD-TDP, type A/B/E had greater absolute WM burden than type C ($p<0.001$). Relative WM burden was greater in FTLD-Tau overall than FTLD-TDP ($p<0.001$). Of FTLD-Tau subtypes, CBD, PSP and PiD all had greater relative WM burden than FTLD-TDP ($p\leq0.001$). Compared to FTLD-TDP subtypes, CBD and PSP had higher relative WM burden than FTLD-TDP type C ($p<0.001$) and type A/B/E ($p<0.013$), while PiD and *MAPT*-mutation carriers had higher relative WM burden than FTLD-TDP type C ($p<0.001$). WM pathology showed region-specific patterns in both proteinopathies ($p<0.001$), with greatest relative WM burden in superior temporal gyrus in FTLD-Tau and mid-frontal cortex in FTLD-TDP. These patterns of divergent pathology distribution were consistent in both bvFTD and PPA clinical subgroups.
Conclusions: FTLD-Tau subgroups share the distinctive feature of greater relative WM pathology differing from FTLD-TDP. There may be regional differences in the distribution of tau and TDP-43 proteinopathy in WM irrespective of clinical FTD syndrome. These findings suggest *in vivo* WM biomarkers may have diagnostic value for molecular pathology in clinical forms of FTLD.

Disclosures: L. Giannini: None. **S. Xie:** None. **D.A. Wolk:** None. **E.B. Lee:** None. **M. Grossman:** None. **J.Q. Trojanowski:** None. **D. Irwin:** None.

Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

Location: Room S106

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 446.11

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

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Title: Treatment with a RIPK1 inhibitor rescues anxiety and cognitive behaviors, calcium dynamics, and reduces tau pathology by altering nitroxidative stress pathways in early-stage progression of a mouse model of frontotemporal dementia

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Abstract: A major challenge in the treatment of tauopathies is identifying the pathogenic molecular mechanisms driving these diseases. Targeted, small molecular inhibitors have ushered new understanding of these mechanisms and potential therapeutic strategies with promising successes. One example, GSK2606414 (GSK414), offers neuroprotection in the rTg4510 mouse model of frontotemporal dementia (FTD). Recent developments in the molecular targets of GSK414 show strong inhibition of RIPK1, a major regulator of necroptosis that strongly correlates with the progression of Alzheimer's disease (AD) pathology. Here, we treated rTg4510 mice before activation of previously confirmed targets of GSK414 to assess the effects of inhibiting RIPK1 in early-stage tauopathy. Our data using behavioral tests that include open-field and Y-maze along with measures of direct, calcium-related brain function, as measured through a novel usage of manganese-enhanced MRI (MEMRI)-delta R1 mapping, show that GSK414 treatment is neuroprotective. GSK414 treatment also diminished tau pathology and nitroxidative stress, which is a toxic feature not yet reported in this model. We further show that GSK414 rescues alterations in mitochondrial function before the onset of severe cognitive impairment and neuronal atrophy as detected through microarray sequencing and quantitative TMT-labeled proteomics, suggesting a new therapeutic window for the treatment of these diseases. Overall, we show the first reported evidence that treatment with a RIPK1 inhibitor provides remarkable benefit in early-stage progression of tauopathy.

Disclosures: **S.A. Koren:** None. **S.E. Meier:** None. **M. Hamm:** None. **R.A. Cloyd:** None. **A. Wilson:** None. **B. Weiss:** None. **M. Bell:** None. **S. D'Alton:** None. **C. Lanzillotta:** None. **S.M.E. Galvis:** None. **F.D. Domenico:** None. **D. Powell:** None. **M. Vandsburger:** None. **J. Chen:** None. **H. Zhu:** None. **J.F. Abisambra:** 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.; Contract with GlaxoSmithKline who especially provided the drug used in the study..

Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

Location: Room S106

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 446.12

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

Support: NIH Grant R21 AG058282
NIH Grant R01 NS077239
NIH Grant R01 AG032611

Title: Neuronally expressed anti-tau scFvs and sdAbs prevent tauopathy-induced phenotypes in *Drosophila* models

Authors: I. S. MARCHAL[1], H. W. HUANG[2], S. KRISHNASWAMY[1], H. D. RYOO[2], *E. M. SIGURDSSON[3];
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Abstract: We are investigating the therapeutic potential of multiple anti-tau antibodies (Abs) in tauopathy models of *Drosophila*, including single chain variable fragments (scFvs) and single domain Abs (sdAbs). First, we showed scFv efficacy in two transgenic (Tg) tauopathy *Drosophila* models, Tau^{WT} and Tau^{R406W}. Both models expressed tau via a neuronal driver, elav-Gal4. scFvs were identified from phage display libraries and once characterized, a promising scFv was expressed in the fly and crossed to both Tau^{WT} and Tau^{R406W} flies. Survival curve analysis revealed highly significant group differences ($p<0.0001$, $n=490$), as both tau models had markedly shorter lifespan than controls ($p<0.0001$), which was dramatically increased upon co-expression of scFv (Tau^{R406W}-scFv: $p<0.0001$; Tau^{WT}-scFv: $p=0.0035$). Further biochemical analyses at different ages revealed extensive age-associated neurotoxicity in both Tau^{WT} and Tau^{R406W} flies ($p=0.0187$-<0.0001) that was inhibited by the scFv ($p=0.0472$-0.0004). Preliminary studies also indicated an association between scFv-mediated prevention of neurotoxicity and extensive tau clearance.
sdAbs are smaller than scFvs, easier to engineer, and typically have higher affinity for their target. Produced by camelids and lacking a light chain, sdAbs' small size (13 kDa) facilitates brain entry, binding to cryptic epitopes, and use for gene therapy. RNA from plasma polymorphonuclear cells was isolated from a llama immunized with full-length recombinant tau, and a phage display library of the sdAb clones was developed and screened. Numerous high affinity sdAb clones were identified with unique binding regions that recognize various forms of

human tau, and several Tg anti-tau sdAb flies have been produced. These sdAb flies are currently being crossed to tauopathy flies. The first sdAbs that have been examined robustly enhanced tauopathy fly survival ($p<0.0001$), and prevented tau-induced developmental lethality ($p=0.0003$). We are now assessing several other anti-tau sdAbs in the same capacity to determine relative efficacy, as well as exploring the cellular and molecular mechanisms involved. Smaller Ab fragments such as scFvs and sdAbs have great potential for therapeutic and diagnostic use, and their humanized anti-tau versions that target various epitopes will likely enter clinical trials in the near future, possibly as gene therapies.

Disclosures: I.S. Marchal: None. **H.W. Huang:** None. **S. Krishnaswamy:** None. **H.D. Ryoo:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a patent application assigned to NYU.

Nanosymposium

446. Tau Protein in Alzheimer's Disease and Other Dementia: Biochemistry and Cellular/Animal Models

Location: Room S106

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 446.13

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

Title: Active immunization with tau epitope in a mouse model of tauopathy induced strong antibody response together with improvement in short memory and tau pathology

Authors: *A. JOLY AMADO[1], H. DAVTYAN[2,3], K. SERRANEAU[4], P. JULES[4], K. ZAGORSKI[5], T. ANTONYAN[5], M. N. GORDON[6], D. H. CRIBBS[7], N. PETROVSKY[8], M. G. AGADJANYAN[5], A. GHOCHIKYAN[5], D. G. MORGAN[9];
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Abstract: Abnormal tau hyperphosphorylation and its aggregation into neurofibrillary tangles are a hallmark of tauopathies, neurodegenerative disorders that include Alzheimer’s disease (AD). Active and passive Tau-immunotherapy has been proposed as a therapeutic approach to AD with mix results. One of the limitations of active immunotherapy may be associated with mediocre immunogenicity of vaccines that are not inducing therapeutically potent titers of antibodies. The aim of this study was to test the efficacy of an anti-tau vaccine, AV-1980R/A composed of N terminal peptide of this molecule fused with an immunogenic MultiTEP platform

and formulated in a strong adjuvant, Advax^{CpG} in a Tg4510 mouse model of tauopathy. Experimental mice were immunized with AV-1980R/A and a control group of mice were injected with adjuvant only. Nontransgenic and tetracycline transactivator (tTA) transgenic littermates were included as baseline controls to contrast with the tau phenotype. Active immunization with AV-1980R/A induced very strong anti-tau humoral immune responses in both nontransgenic and transgenic mice with evidence of IgG in brains of AV-1980R/A vaccinated mice. These experimental animals displayed an improvement in short-term memory during a novel object recognition test. However, impairments in other behavioral tasks were not prevented by AV-1980R/A vaccinations. At the same time, high titers of anti-tau antibodies reduced hyperphosphorylated pSer396 tau, but not lowered level of other phosphorylated tau in the brains of AV-1980R/A vaccinated mice. These data indicate that active immunotherapy with an N-terminal Tau epitope was only partially effective in improving cognition and reducing pathology in a stringent Tg4510 mouse model of tauopathy.

Disclosures: **A. Joly Amado:** None. **H. Davtyan:** None. **K. Serraneau:** None. **P. Jules:** None. **K. Zagorski:** None. **T. Antonyan:** None. **M.N. Gordon:** None. **D.H. Cribbs:** None. **N. Petrovsky:** None. **M.G. Agadjanyan:** None. **A. Ghochikyan:** None. **D.G. Morgan:** None.

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.01

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

Support: NIH Grant AG057767
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Center for Alzheimer’s Disease and Related Disorders at SIU School of Medicine
Kenneth Stark Endowment
Fraternal Order of Eagles
SIU School of Medicine Foundation

Title: The effects of Riluzole treatment on glucose metabolism, insulin sensitivity, and cognition in male and female mouse models of normal aging and Alzheimer’s disease

Authors: *C. A. FINDLEY[1,2], N. ESPERANT-HILAIRE[1], K. N. HASCUP[1,2,3], E. R. HASCUP[1,2];
[1]Neurology, Neurosci. Institute, Ctr. for Alzheimer's Dis., [2]Pharmacol., [3]Med. Microbiology, Immunology, and Cell Biol., Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: Alzheimer’s Disease (AD) is characterized by accumulation of soluble amyloid beta $(A\beta)_{42}$ and hyperphosphorylated tau protein. Previous work from our laboratory demonstrated

that prodromal Riluzole treatment, a Food and Drug Administration approved drug for amyotrophic lateral sclerosis, decreases glutamatergic tone in the transgenic AβPP/PS1 mouse model of AD. Additionally, Riluzole treated AβPP/PS1 mice undergoing cognitive evaluation using the Morris water maze (MWM) spatial learning and memory task perform at age- and sex-matched C57BL/6 genotypic control levels, supporting a procognitive effect. In this study, the $APP^{NL-F/NL-F}$ knock-in mouse model of AD was utilized to further elucidate the role of $A\beta_{42}$. $APP^{NL-F/NL-F}$ mice have elevated $A\beta_{42}$ levels without overexpression of amyloid precursor protein, but with similar disease progression to AβPP/PS1 mice. Age-matched vehicle treated C57BL/6 mice were included as genetic background controls. Male and female C57BL/6 and $APP^{NL-F/NL-F}$ mice received either vehicle (1% sucrose) or Riluzole (356 µM) treated drinking water (voluntary oral administration) between 2-6 months of age. At 12 months, mice underwent insulin and glucose tolerance testing (ITT, GTT) followed by an 8-day MWM (five consecutive trial days and a single probe trial) to test cognition. Preliminary metabolic data support that vehicle-treated and Riluzole-treated male C57BL/6 (n=5-6) and $APP^{NL-F/NL-F}$ (n=5) are less insulin sensitive compared to treatment-matched females C57BL/6 (n=4-9) and $APP^{NL-F/NL-F}$ (n=5-6), respectively. A trend of male Riluzole-treated mice showed increased insulin sensitivity compared to genotype-matched vehicle mice was also observed. Conversely, vehicle-treated female mice tended to have impaired glucose metabolism compared to treatment-matched males, an opposing trend to that observed with Riluzole-treated groups. Preliminary observations do not show differences in cognitive performance between sexes of the same genotype or between treatment groups during learning or memory phases. However, sucrose-treated $APP^{NL-F/NL-F}$ males tended to have decreased memory retrieval compared to sucrose-treated C57BL/6 males, supporting previous observations that prodromal Riluzole treatment may prevent and/or delay cognitive decline in AD. Thus, preliminary data from $APP^{NL-F/NL-F}$ mice builds upon previous data from transgenic AβPP/PS1 mice and supports a potential impact of sex on insulin sensitivity and glucose metabolism. Studies to further elucidate the mechanisms and impacts of prodromal Riluzole treatment in AD mice are ongoing.

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Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.02

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

Support: University grants commission, New Delhi

Title: Imperatorin ameliorates diabetes associated cognitive decline, modulates oxidative stress and acetylcholinesterase levels in mice

Authors: *A. JUVEKAR, A. CHOWDHURY, S. CHANDA, J. BATGIRE, S. PAI;
Inst. of Chem. Technol., Mumbai, India

Abstract: Patients with diabetes mellitus are at an increased risk for the development of Alzheimer's disease (AD). Recent literature reveals many similarities between the molecular pathways associated in the pathogenesis of both the diseases. Imperatorin (IMP), a naturally occurring furanocoumarin, has reported antidiabetic and neuroprotective activity. The present study examines the anti-amnesiac and neuroprotective activity of oral (*po*) administration of IMP in diabetes associated cognitive decline (DACD). Streptozotocin (STZ) 155 mg/kg was injected intraperitoneally (*ip*) to induce diabetes. Metformin (MFN) (500 mg/kg) was employed as a positive standard. Morris water maze (MWM) and Y-maze were used to evaluate the spatial and working memory respectively. Lipid peroxidation and markers of oxidative stress such as superoxide dismutase (SOD) and reduced glutathione (GSH) were evaluated. Also, cholinergic involvement was assessed by measuring the levels of acetyl cholinesterase (AChE). Chronic treatment with IMP (5 and 10 mg/kg *po* once daily) and MFN for 30 days lowered the blood glucose levels in diabetic mice. The DACD was observed to be ameliorated significantly in both MWM and Y-maze as compared to STZ group. Moreover, oxidative stress was significantly decreased as higher levels of SOD, GSH and lowering of lipid peroxidation was observed in IMP and MFN treated animals as compared to STZ treated mice. Also, significant lowering of AChE was observed in the IMP and MFN treated groups as compared to STZ treated group. In conclusion, the present study demonstrates that IMP supplementation may be beneficial in the treatment of DACD due to its effects on AChE and oxidative stress.

Disclosures: A. Juvekar: None. **A. Chowdhury:** None. **S. Chanda:** None. **J. Batgire:** None. **S. Pai:** None.

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.03

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

Support: Grant-in-Aid for Young Scientists (JSPS KAKENHI Grant Number 19K16288)

Title: Diosgenin improves memory deficits in a mouse model of Alzheimer's disease by promoting axonal regrowth in the brain

Authors: *X. YANG, C. TOHDA;
Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan

Abstract: Alzheimer's disease (AD) is a progressing neurodegenerative disorder developed by deposition of Aβ and its subsequent disruption of neural networks in the brain. We consider that it is important to restore neural circuits for recovery of memory function in AD. We previously found that diosgenin, a constituent of Dioscorea Rhizoma, restored Aβ-induced axonal atrophy in neurons (*in vitro*) and improved memory function in a mouse model of AD, 5XFAD. Although no studies have demonstrated that degenerated axons regrow again toward their intrinsic target in AD brains, we hypothesized that proper circuits would be reconstructed by diosgenin in AD brain. Therefore, in this study, we investigated whether diosgenin promotes proper axonal regrowth in 5XFAD brains, and clarify the mechanisms for accurate pathfinding of axons in adult brains. At first, axonal regrowth effect of diosgenin *in vivo* was investigated using cortex-axotomized mice. Oral administration of diosgenin for 15 days significantly promoted axonal regrowth in the axotomized brain area. Next, we focused on a long distance axonal projection in the circuit for memory formation; the hippocampus to the prefrontal cortex. Retrograde tracing revealed that axonal projections from the hippocampus to the prefrontal cortex significantly decreased in 5XFAD compared to wild-type mice. However, 14-day administration of diosgenin to 5XFAD mice significantly increased axonal projections in this circuit. At this time, object recognition memory of 5XFAD mice was significantly improved by diosgenin administration. After that, naïve neurons and axon-regrew neurons in the brain were captured by laser microdissection, and changed genes in expression level were analyzed by microarray. Several molecules were identified as key candidates of axonal reconnection to its intrinsic targets in AD brains. Our study suggests for the first time that degenerated axons in AD brains have capacities to regrow toward their intrinsic target neurons. Furthermore, diosgenin may be a promising drug to remodel neural circuits by promoting axonal regrowth and recover memory function in AD. This finding proposes a novel therapeutic strategy to promote axonal regrowth for AD treatment.

Disclosures: X. Yang: None. **C. Tohda:** None.

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.04

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

Support: NIH AG044332

Title: Microtubule-stabilizing agents reduce aβ plaque burden and plaque-associated axonal dystrophy in 5XFAD mice

Authors: S. MAIMAITI[1], P. KOIVULA[1], K. OUKULOFF[2], Y. YAO[1], V. LEE[1], A. SMITH III[3], J. TROJANOWSKI[1], C. BALLATORE[2], ***K. R. BRUNDEN**[1];
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Abstract: The hallmark pathologies within Alzheimer's disease (AD) brain are extracellular senile plaques comprised of Aβ peptides and intra-neuronal inclusions containing tau protein. It has been hypothesized that Aβ plaque deposition, which occurs many years before symptomology, initiates a series of events that ultimately promotes tau pathology and neuronal death. Tau normally binds to axonal microtubules (MTs), where it appears to stabilize distal regions of MTs, and in AD tau becomes hyperphosphorylated and disengages from MTs with subsequent inclusion formation. This is thought to increase MT dynamics and impair axonal transport, contributing to neuronal dysfunction. We previously demonstrated that treatment of tau transgenic (Tg) mice with brain-penetrant MT-stabilizing agents results in normalized MT density and axonal transport, with a corresponding reduction in tau pathology, synapse loss, and neuronal death. Notably, MT deficits are not only observed with tau pathology, but are also seen in dystrophic neuronal processes that are associated with Aβ plaques in AD brain and in Aβ plaque-bearing Tg mice. These plaque-associated neuronal MT deficits may impair local axonal transport and explain the observed accumulation of APP, BACE1, kinesin and other proteins in the swollen axonal processes. We have recently administered MT-stabilizing agents to young 5XFAD Tg mice that develop robust Aβ plaque burden in the brain with age. Notably, the MT-stabilizing agents epothilone D (EpoD) and CNDR-51657 both caused significant reductions of plaque-associated APP-positive dystrophic processes in 5XFAD mice relative to vehicle-treated 5XFAD mice (n=5-6/treatment). Moreover, Aβ plaque development was significantly diminished in the 5XFAD mice treated with either EpoD or CNDR-51657. These results suggest a vicious cycle whereby initial Aβ plaque formation leads to the disruption of MTs in nearby axonal processes, resulting in the accumulation of APP and enzymes that facilitate additional Aβ generation and fulminant plaque deposition. Importantly, these data reveal that brain-penetrant MT-stabilizing agents can reduce both Aβ and tau pathologies, and such molecules hold promise as AD therapeutics.

Disclosures: S. Maimaiti: None. **P. Koivula:** None. **K. Oukuloff:** None. **Y. Yao:** None. **V. Lee:** None. **A. Smith III:** None. **J. Trojanowski:** None. **C. Ballatore:** None. **K.R. Brunden:** None.

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.05

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

Support: NeuroBo
Dong-A

Title: Tapping the potential of herbal botanicals as treatment for Alzheimer's disease

Authors: *K. V. KASTANENKA[1], M. SOHN[2], S. CHOI[2], H. GO[2], B. J. BACSKAI[1]; [1]Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA; [2]Dong-A, Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by deposition of amyloid plaques and formation of intracellular neurofibrillary tangles, resulting in a progressive memory loss and cognitive decline. The molecular mechanisms driving these pathologies are potential targets for development of AD treatments. We studied the effects of NB-02, earlier known as DA-9803, a multimodal botanical cocktail in a transgenic mouse model of AD, APP/PS1 mice. Longitudinal imaging using multiphoton microscopy allowed monitoring of the extracellular senile plaques and intracellular neuronal calcium levels. Cytosolic calcium is an indirect marker of neuronal activity and is normally tightly regulated. Our past research has shown that resting calcium is elevated in a fraction of neurites in APP transgenic mice. Thus, an effective treatment would restore calcium to control levels. 100 mg/kg NB-02 was administered daily to 10 month-old APP/PS1 mice via a gavage treatment for 2 months. Longitudinal imaging was performed before and during the treatment. Plaques were labeled with methoxy-XO4 while intraneuronal calcium levels were measured with the genetically encoded calcium sensor Yellow Cameleon 3.6 (YC3.6). Chronic administration of NB-02 halted amyloid plaque deposition over the 2 months treatment period in these mice. Elevated calcium was detected in a subset of neurons before treatment. NB-02 restored the elevated neuronal calcium to control levels over this time course. Treatment with a vehicle cocktail failed to decrease the rate of plaque deposition or restore intracellular calcium. In summary, these results demonstrate that treatment of old APP/PS1 mice with 100 mg/kg NB-02 halts deposition of amyloid plaques and restores neuronal calcium homeostasis. Thus, NB-02 treatment could have a restorative effect on neuronal function in AD.

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Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.06

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

Support: CIHR Grant / PJT 156242
SynAD/ RES 0045841

Title: Protective effect of A_{11} gold nanoparticles against aggregation and toxicity mediated by β-amyloid: Potential implications for Alzheimer's disease

Authors: *B. G. ANAND[1], Q. WU[2], K. SHEJALE[5], S. AMIDIAN[3], H. WILLE[4], S. KAR[1]; [1]Med., [3]Biochem., [4]Ctr. for Prions and Protein Folding Diseases, Univ. of Alberta, [2]Univ. of Alberta, Edmonton, AB, Canada; [5]Dept. of Metallurgical Engin. and Materials Sci., Indian Inst. of Technol., Bombay, Powai, India, India

Abstract: Evidence suggests that increased aggregation of beta-amyloid (Aβ) peptides initiates neurodegeneration and subsequent development of Alzheimer's disease (AD). At present, there is no effective treatment for AD. Recently, some studies focused on developing small molecules, including conjugated-nanoparticles, that can prevent Aβ aggregation as a treatment strategy for AD, but little is known on surface engineered stealth-based nanoparticles. Thus, we synthesized phenolic A11 compound-based 5nm sized gold nanoparticles (AuNPs) that can attenuate Aβ aggregation and/or neurotoxicity. In vitro aggregation kinetic assays for $Aβ_{1-42}$ were carried out using Thioflavin-T in presence or absence of newly synthesized AuNPs. Various biophysical techniques such as Circular dichroism, Fourier Transform Infra-Red, and Raman spectroscopy as well as Dynamic Light Scattering were employed to evaluate the inhibitory effect of AuNPs on $Aβ_{1-42}$ aggregation. The samples were further characterized by Electron Microscopy. To determine the bio-affinity of A_{11} nanoparticles for $Aβ_{1-42}$, we performed Fluorescence quenching and Isothermal Titration Calorimetry (ITC) experiments, which were validated using molecular docking tools. Additionally, using mouse cortical cultured neurons, the effects of AuNPs on $Aβ_{1-42}$-mediated toxicity were evaluated. Our thioflavin kinetics data confirmed that these polycrystalline AuNps were able to suppress the spontaneous and seed-induced aggregation of $Aβ_{1-42}$. Interestingly, such an effect was not observed for unfunctionalized A_{11} molecules or control AuNps. Molecular docking, Fluorescent Quenching, and ITC data clearly revealed a strong interaction between monomeric $Aβ_{1-42}$ and A_{11} AuNps. Moreover, AuNps were found to protect mouse cultured neurons against Aβ-induced toxicity by regulating kinases underlying phosphorylation of tau protein. Thus, we have successfully functionalized a new phenolic compound-based gold nanoparticle, which can suppress the aggregation of $Aβ_{1-42}$ by interacting with amyloidogenic residues and protect cultured neurons against toxicity - highlighting its

potential therapeutic implications in the treatment of AD-related pathologies.
Key words: Alzheimer disease, Gold nanoparticles, Amyloid beta, Tau phosphorylation, Phytochemicals

Disclosures: **B.G. Anand:** None. **Q. Wu:** None. **K. Shejale:** None. **S. Amidian:** None. **H. Wille:** None. **S. Kar:** None.

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.07

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

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Title: Memory impairments and synaptic failure in Tg19959 AD model mice are alleviated by eEF2K inhibitor A-484954

Authors: *N. KASICA, W. YANG, X. ZHOU, T. MA;
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Abstract: Mounting evidence indicates synaptic failure as an early and key event in Alzheimer’s disease (AD) pathophysiology. Maintenance of long-term memory and synaptic plasticity requires *de novo* (from new) protein synthesis. Phosphorylation of mRNA translation factor eukaryotic elongation factor 2 (eEF2) by its kinase eEF2K results in inhibition of general protein synthesis. Previous studies have shown elevated levels of eEF2 phosphorylation in *post-mortem* AD human brain tissue and in AD mouse models. We recently reported that genetic suppression of eEF2K can prevent cognitive impairments in AD model mice. However, whether eEF2K inhibition presents therapeutic potential in aged mice with cognitive defects already developed is unknown. Here we investigated whether suppression of eEF2 phosphorylation via eEF2K inhibitor A-484954 can reverse synaptic failure and memory impairments in Tg19959 AD model mice. Aged Tg19959 mice (6-9 months) and littermate controls were injected with a subcutaneous pellet containing either 2.625 mg A-484954 or vehicle. The pellet continuously releases drug over 30 days. Starting two weeks after pellet injection, the mice underwent cognitive assessment via the Novel Object Recognition, Morris Water Maze, and Passive Avoidance tasks to assess learning and memory. We found that cognitive impairments displayed in aged Tg19959 mice were alleviated with treatment of A-484954. Furthermore, *de novo* protein

synthesis rates were assessed via the surface sensing of translation (SUnSET) assay, and it was found that impaired *de novo* protein synthesis in hippocampi of Tg19959 mice was rescued with A-484954 treatment. Taken together, our results suggest that treatment with a eEF2K inhibitor, A-484954 alleviates cognitive impairments and restores translational capacity in a mouse model of AD.

Disclosures: **N. Kasica:** None. **W. Yang:** None. **X. Zhou:** None. **T. Ma:** None.

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.08

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

Support: 1T32AG057468-01

Title: Evidence for attenuation of BBB-dysfunction via calpain-cathespin inhibition strategies relevant to TBI and ADRD

Authors: ***R. C. KNOPP**[1], A. JASTANIAH[1], O. DUBROVSKYI[2], S. H. LEE[1], L. M. TAI[3], G. R. J. THATCHER[1,2];
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Abstract: The calpain-cathepsin hypothesis (CCH) predicates elevation of calpain-1 (CAPN1) and cathepsin-B (CTSB) as an underlying mechanism in the pathogenesis of Alzheimer’s disease (AD) and related dementia, traumatic brain injury (TBI), and ischemic stroke. The hypothesis is supported by studies with small molecule inhibitors, such as NYC-438, that reduce cognitive deficits in AD mouse models. Though they display efficacy, NYC-438, a nonselective CAPN1/CTSB inhibitor and selective CAPN1 inhibitors reported in the literature exhibit poor brain bioavailability. We hypothesized that the CCH could account for dysfunction of the blood-brain barrier (BBB) and, in particular, brain endothelial cell (BEC) dysfunction. To test this theory and further characterize selective vs nonselective targeting of CAPN1 vs CTSB, we developed selective small molecule inhibitors, and characterized both their neuroprotective efficacy in *in vitro* ischemia-reperfusion injury and neuroinflammatory attenuation in an *in vivo* mTBI mouse model of oxidative-stress (OS). Various inhibition strategies provided the expected dose-dependent neuroprotection in primary neurons and mitigated the post-mTBI neuroinflammatory surge seen in the OS-mouse model. We then isolated BECs from WT and OS mice and saw enhanced susceptibility in the OS-BECs after ischemia-reperfusion injury, suggesting a role for oxidative stress and lipid peroxidation in exacerbating CAPN1/CTSB mediated BBB damage. Moreover, when subjecting BECs from female FAD-Tg mice to OGD,

we saw exacerbated damage in ApoE4 vs. ApoE3 female BECs. This suggests that the ApoE4 allele, the largest genetic known risk factor for AD, confers reduced resilience against oxidative stress injury. BECs from WT, OS, and FAD-Tg mice provide a platform to assess the role of CCH in in cell viability, tight junction proteins, and transendothelial electrical resistance, and provides support for targeting CAPN1/CTSB in protecting the BBB, either in early life trauma, such as TBI, or in ADRD itself.

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Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

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Presentation Number: 447.09

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

Support: R43AG029777
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R44AG053150
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R44AG062021

Title: Selection of a small molecule tau oligomer inhibitor for IND enabling studies

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Abstract: Tau oligomers have been shown to transmit tau pathology from diseased neurons to healthy neurons and are thought to play a causative role in the progression of Alzheimer’s disease and related dementias (ADRD). Our therapeutic approach is based on the premise that tau oligomers are the acutely toxic aggregated species of tau and their reduction will modify the course of ADRD. Here, we present studies supporting the selection of the lead candidate.
This small molecule program differentiates itself by targeting tau self-association into oligomers, at the beginning of the tau aggregation cascade, to inhibit all downstream tau aggregation events, whereas other approaches have focused on targeting the formation of tau fibrils or disrupting them.
In vivo efficacy of the lead compound in blinded studies in the htau mouse model of tauopathy demonstrated that inhibiting tau self-association can also reduce the formation of insoluble tau aggregates. Evaluations of dose exposure levels showed that the efficacy data had a linear dose

response and affected phosphorylation at multiple sites in tau. There were no adverse events related to treatment with the compound. The activity translated from *in vitro* and cellular assays to an *in vivo* model of tau aggregation, thereby validating our screening approach and showing that targeting oligomer formation can inhibit the entire tau aggregation pathway.
In vitro pharmacology studies have shown good metabolic stability and a favorable safety profile including no mutagenicity in a mini-AMES test. Preliminary (non-GLP) safety studies were performed in rats. The maximum tolerated dose was 1,000 mg/kg, and there was no apparent toxicity in a 14-day dose range finding study. We scaled up synthesis for non-clinical safety studies of this CNS drug-like lead. This work has de-risked the performance of IND enabling studies and supports the success of the lead candidate in the clinic.

Disclosures: **E.J. Davidowitz:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P. Lopez:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc.. **H. Jimenez:** None. **L. Adrien:** None. **P. Davies:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **J.G. Moe:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc..

Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.10

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

Support: R01 AG059799
R01 MH107659-03
T-PEP-18-579974

Title: PDDC: A novel neutral sphingomyelinase 2 inhibitor for the treatment of Alzheimer’s disease

Authors: *C. TALLON[1], K. HOLLINGER[1], M. SALA[2], R. DASH[1], A. G. THOMAS[3], A. DATTA CHAUDHURI[1], A. KUMAR[1], L. E. LOVELL[4], Y. WU[1], R. RAIS[1], N. J. HAUGHEY[5], R. NENCKA[2], C. ROJAS[1], B. S. SLUSHER[6];
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Abstract: Alzheimer's disease (AD) is a disease affecting older patients resulting in extensive memory loss for which there are currently no satisfactory treatments. As the population ages, the economic burden of AD is poised to increase, highlighting the importance of identifying effective treatments. Evidence is mounting supporting the propagation of toxic proteins, like tau and amyloid, in a "prion-like" manner as a possible mechanism for the progressive declining cognitive function. This spreading of tau appears to be along connectivity pathways in both humans and animal models. This may be potentially mediated by "infected" neurons and glial cells packaging tau into exosomes and transferring it to healthy neurons and glial cells. Neutral sphingomyelinase 2 (nSMase2), which catalyzes the hydrolysis of sphingomyelin to produce phosphorylcholine and ceramide, is important for exosome biogenesis. By reducing exosome production, this toxic spreading of tau may be reduced, thus slowing down the disease progression. Indeed, several laboratories have demonstrated that when nSMase2 function is reduced in AD mouse models, either pharmacologically or genetically, cognition is markedly improved with a reduction in the spread of tau. Unfortunately, there are no clinically available nSMase2 inhibitors. Following a high-throughput screening assay and extensive structure-activity relationship studies, we identified phenyl (R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b] pyridazin-8-yl) pyrrolidin-3-yl) carbamate (PDDC), a nM potent inhibitor with excellent selectivity, oral bioavailablility, and brain penetration. PDDC inhibits exosome release in both *in vitro* and *in vivo* assays. Additionally, chronic daily PDDC treatment in 5XFAD mice (10mg/kg) improved cognitive function in the contextual fear conditioning assay. We are building on this preliminary data by expanding our testing to tauopathy mouse models of AD. If successful, PDDC would represent a novel compound targeting the pathological spread of toxic proteins in AD.

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Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.11

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

Support: NIh, AG-008200
NIH, 2R01-NS047229

NIH, P50AG05138

Title: Neurodegenerative mechanisms of AD maybe independent of pathological hallmarks

Authors: *N. K. ROBAKIS[1], M. A. RAHIM[2], Y. YOON[3], Z. SHAO[2], C. DIMOVASILI[4], A. GEORGAKOPOULOS[2];
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Abstract: Alzheimer's disease (AD), the most common cause of dementia, is caused by severe neurodegeneration in the hippocampus and neocortical regions of the brain but the cause of this neuronal loss is unclear. Current theories of AD are mainly based on the hypothesis that pathological hallmarks used to define AD, such as insoluble (amyloid) and soluble derivatives of Aβ peptides or abnormal aggregates of tau protein, are also causative agents of AD. These theories form the basis of most current therapeutic approaches to AD. Importantly however, empirical observations and experimental data are inconsistent with the amyloid/Aβ theories of AD [Robakis and Neve (1998), TINS vol. 21 pp.15-19; Robakis (2011) NBA vol. 32, pp 372-379]. Similarly, evidence suggests that tau abnormalities may not play a crucial role as causative agents of AD neurodegeneration. It thus remains unclear that targeting pathological hallmarks are productive therapeutic approaches for AD. We hypothesize that neurodegenerative diseases such as AD target biological functions of factors involved in neuroprotective pathways. To test our theory we used KI mouse models expressing heterozygous PS1 FAD mutants as these have similar genotypes as FAD patients and may serve as models to test neurodegenerative mechanisms. We found that following Middle Cerebral Artery Occlusion (MCAO)-induced brain ischemia, PS1FAD mutants M146V and I213T have dominant negative effects on neuronal survival and behavior in the absence of amyloid or tau pathologies. Furthermore, these PS1 FAD mutants interfere with the neuronal ability to use neurotrophins, such as BDNF, neuroprotectively in response to toxic insults. Our data also show that FAD mutants impair NMDAR-mediated evoked excitatory presynaptic currents (EPSC) in hippocampal slices in the absence of plaques or tangles. In summary, our data indicate that factors causing AD type of dementia, such as FAD mutants, can increase toxicity-induced neuronal death and dysfunction independent of neuropathological hallmarks such as amyloid and tau. Furthermore, our data suggest a mechanism by which FAD mutants increase neuronal death by decreasing neurotrophin-dependent neuroprotection. Combined with genetic data, our findings support the hypothesis that FAD mutants may cause neurodegeneration and AD by affecting critical functions of the WT parent proteins in brain neuroprotective mechanisms

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Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.12

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

Support: Insys Therapeutics

Title: The effects of low dose THC as a treatment for APP/PS1 mice

Authors: Y. HONG[1], X. LIN[1], B. BROWN[1], X. LI[1], J. CAI[1], D. MORGAN[2], M. GORDON[2], ***C. CAO**[1];
[1]Univ. of South Florida, Tampa, FL; [2]Michigan State Univ., Grand Rapids, MI

Abstract: Previously, we have demonstrated that extremely low doses of THC may be a potential therapy for Alzheimer's disease in the N2a/APPswe cell line. Here, we have identified the potential mechanism of THC as a treatment for AD in the paper. We completed an *in vivo* study by treating APP/PS1 mice bi-weekly by intraperitoneal injection with low THC doses. Mice were divided into three different groups (non- treatment control, 0.2 mg/kg THC treatment group and 0.02 mg/kg THC treatment group). Mice were tested pre-treatment using the radial arm water maze test and blood was collected to test blood Aβ levels. Mice were tested again post-treatment to monitor any treatment benefit. Both latency and errors significantly improved in the THC treatment groups compared to the transgenic control group. However, there are no significant Aβ level changes among all transgenic groups. However, there are no significant differences among the transgenic mice groups in Aβ40, or 42 levels in plasma and brain. Also, there is no significant change in Aβ levels shown in the immunostaining results in any region of the brain tissues tested. Cytokine expression profile detection revealed that there are no differences among the groups as well. However, the flow cytometry results showed a trend that THC treatment tends to increase central memory T-cell populations (CD62L+/CD127+). CD8a+/CD11c+ DCs show an increase post treatment in the 0.2 mg/kg treatment group compared to the transgenic control group. The overall memory benefit of THC treatment can be seen through an immune modulation effect, so a more detailed analysis is required to draw any definitive conclusions.

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Nanosymposium

447. Alzheimer's Disease and Related Dementia: Therapeutic Strategies

Location: Room S103

Time: Tuesday, October 22, 2019, 8:00 AM - 11:15 AM

Presentation Number: 447.13

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

Support: CNPq
FAPERJ
CAPES
CONICET
INNT
ISN
The Company of Biologists

Title: Neuronal expression of NUsc1, a single-chain variable fragment antibody against abeta oligomers, protects synapses and rescues memory in Alzheimer's disease models

Authors: *M. SELLES[1], J. FORTUNA[1], M. CERCATO[2], A. BITENCOURT[3], A. SOUZA[1], H. JANICKOVA[5], J. DE SOUZA[6], S. ALVES-LEON[6], V. F. PRADO[7], M. A. PRADO[8], A. EPSTEIN[9], A. SALVETTI[9], A. S. SEBOLLELA[4], O. ARANCIO[10], W. L. KLEIN[11], F. DE FELICE[1], D. JERUSALINSKY[2], S. T. FERREIRA[12];
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Abstract: Alzheimer’s disease (AD) is the main cause of dementia in the elderly and is characterized by abnormal accumulation of the amyloid-β peptide (Aβ) in the brain. Considerable evidence implicates soluble Aβ oligomers (AβOs) in synapse dysfunction and memory loss in AD. Here, we have investigated the neuroprotection conferred by neuronal expression of NUsc1, a single-chain variable fragment (scFv) antibody that specifically targets AβOs, with low reactivities against Aβ monomers and fibrils. Purified recombinant NUsc1 prevented AβO-induced inhibition of synaptic plasticity in hippocampal slices and blocked memory impairment in mice that received an intracerebroventricular (i.c.v.) infusion of AβOs. Sustained neuronal expression of NUsc1 was achieved using an adenoassociated virus-derived vector (AAV-NUsc1). AAV-mediated NUsc1 expression significantly reduced AβO binding to hippocampal neurons in culture, and prevented AβO-induced loss of dendritic spines. In vivo, AAV-NUsc1 induced brain expression and secretion of NUsc1, and rescued memory in aged APPswe/PS1dE9 AD model mice and in wild type mice that received an i.c.v. infusion of AβOs. Finally, AAV-NUsc1 induced NUsc1 expression in adult human brain slice cultures. Results suggest that AAV-NUsc1 may represent a potential tool for gene therapy aimed at preventing synapse damage and memory defects in AD.

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Nanosymposium

448. Stroke I

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Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 448.01

Topic: C.08. Ischemia

Support: R21NS098514
R01NS44025
R01NS76726

Title: TLR2/CD36 signaling modulates the choroid plexus myeloid cell pool and impacts injury following neonatal stroke

Authors: *A. RAYASAM, J. FAUSTINO, **Z. VEXLER**;
Neurol., Univ. of California - San Francisco, San Francisco, CA

Abstract: Introduction: The expression of CD36 on myeloid cells plays a key role in influencing neuroinflammatory processes. We previously showed that CD36 can be protective by scavenging apoptotic cell debris and quelling NFκB-mediated neuroinflammation following transient middle cerebral artery occlusion (tMCAO) in neonatal mice [(1)]. Furthermore, we have demonstrated that CD36 can function through TLR2 signaling and lead to context-dependent effects after neonatal stroke, sterile inflammation and infection [(2)]. We showed that choroid plexus (CP) myeloid cells express TLR2 during early postnatal development, possibly presenting a unique window for therapeutic intervention. Whereas the CP has been shown to serve as a homing site for immune cells in in adult mice [(3)], little is known about the mechanisms of how CP myeloid cells extravagate the neonatal parenchyma and contribute to disease pathology.
Objective: We characterized the phenotypes of acutely CP-infiltrating myeloid cells after TLR2 ligand stimulation and after neonatal stroke in WT and CD36KO mice. Our long term goal is to understand how targeting TLR2/CD36 influences the choroid plexus myeloid cell pool and how these cells contribute to neonatal ischemic brain pathology.
Methods: We administered TLR1/2 ligand (Pam3CSK4, PAM, 5mg/kg, 6hr i.p.) to p9/10 WT and CD36KO mice or subjected mice to a 3hr tMCAO followed by 3hr reperfusion. We evaluated the presence and phenotypes of myeloid cells in the CP and cortex characterized by flow cytometry and immunofluorescence.
Results: In WT p9/p10 mice, compared to vehicle, PAM administration significantly increased the number of $CD11b^{+}/CD45^{high}/Ly6C^{+}$ inflammatory monocytes and $CD11b^{+}/CD45^{high}/Ly6G^{+}$ neutrophils in the CP (p=0.0001; n=6) and cortex (p=0.0001; n=6). tMCAO also induced accumulation of $CD11b^{+}/CD45^{high}$ inflammatory myeloid cells in the ipsilateral CP (p=0.032; n=5) and ipsilateral cortex (p=0.0001, n=6) as compared to contralateral. In CD36KO mice, the acute number of infiltrating myeloid cells in the CP and cortex was greatly reduced following

PAM treatment compared to WT mice (p=0.001; n=6). In contrast, following tMCAO, the number of peripheral myeloid cells in the ipsilateral CP and cortex was similar in WT and CD36KO mice. **Summary/Conclusions**: Both neonatal stroke and TLR2 stimulation trigger robust accumulation of myeloid cells in the CP leading to context- and brain region-dependent responses. Understanding the migratory patterns and phenotypes of CP-infiltrating myeloid cells with intact and disrupted TLR2/CD36 signaling may potentially guide to novel therapeutic targets to limit injury after neonatal stroke.

Disclosures: A. Rayasam: None. **J. Faustino:** None. **Z. Vexler:** None.

Nanosymposium

448. Stroke I

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Presentation Number: 448.02

Topic: C.08. Ischemia

Support: NSFC

Title: Zinc accumulation in mitochondria promotes blood brain barrier disruption through Drp1 dependent mitochondria fission during cerebral ischemia

Authors: *Z. QI[1], K. LIU[2];
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Abstract: High concentration of zinc has been reported to act as a critical mediator of neuronal death in the ischemic brain. Our previous studies have established that labile zinc accumulates in microvessels and contributes to blood-brain barrier (BBB) permeability increase after cerebral ischemia. However, the role of zinc interaction with mitochondria in ischemia-induced alteration of BBB permeability is still unclear. In this study, we showed that ischemia/reperfusion induced free zinc accumulation in endothelial cells (ECs), resulting in increased generation of reactive oxygen species (ROS) in both cultured ECs and in microvessels isolated from the brain of ischemic rats. Furthermore, we found that zinc was highly accumulated in mitochondria, leading to mitochondrial ROS generation under the ischemic condition. Moreover, zinc overload in mitochondria resulted in the collapse of the network of mitochondria, which was mediated through Dynamin-related protein-1 (Drp-1) dependent mitochondrial fission pathway. Finally, the zinc overload in mitochondria activated matrix metalloproteinase-2 and led to ischemia-induced BBB permeability increase. These cellular and animal studies demonstrate that zinc-ROS pathway in mitochondria contributes to the ischemia-induced BBB disruption via Drp-1 dependent mitochondrial fission pathway.

Disclosures: Z. Qi: None. **K. Liu:** None.

Nanosymposium

448. Stroke I

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Topic: C.08. Ischemia

Support: VA Grant I01BX002891

Title: Correlation of angiotensin II-induced NF-kB transcriptional activation and WNK-SPAK-NKCC1 cascade upregulation in mouse cortical neurons after ischemic stroke

Authors: *M. H. BHUIYAN[1,2], X. DENG[5], J. ZHANG[6], A. C. STRAUB[3], M. B. MINNIGH[4], B. J. MOLYNEAUX[1,2], S. M. POLOYAC[4], D. SUN[1,2,7];
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Abstract: Objectives: Stroke patients with comorbid hypertension have worsened outcome. However, treating acute ischemic stroke patients with blood pressure lowering agents failed to improve outcome. The WNK-SPAK/OSR1 kinase complex regulates function of ion transporters and channels in renal salt handling and plays an important role in the pathogenesis of hypertension. In this study, we investigate whether stimulation of the brain WNK-SPAK-NKCC1 complex leads to worsened ischemic damage in hypertensive mice. **Methods:** Hypertension was induced in C57BL/6J male mice by subcutaneous infusion of 1000 ng/kg/min angiotensin II (Ang II, via mini-osmotic pump) for two weeks. Ischemic stroke was induced by permanent occlusion of the distal branches of the left middle cerebral artery (pdMCAO). Three hours after pdMCAO, mice were randomly assigned to receive either vehicle DMSO (2 ml/kg body weight/day, i.p.) or a novel SPAK inhibitor ZT-1a (5 mg/kg/day, i.p.). Infarct volume, hemisphere swelling, and neurological behavioral deficits were analyzed and expressions of NKCC1, SPAK/OSR1, WNK1-4 or NF-κB proteins were quantified by immunoblot and immunofluorescence staining analyses. **Results:** Hypertensive mice displayed significantly larger infarct and hemispheric swelling at 24 h after pdMCAO, and exhibited slower recovery of neurological function, compared to normotensive control mice. PdMCAO stimulated expression of WNK proteins (isoforms 1, 2, 4), SPAK/OSR1 and NKCC1 proteins (non- and phosphorylated) in ischemic brains of the Ang II-infused hypertensive mice. Increase of nuclear NF-κB protein level, nuclear translocation of phospho-NF-kB protein, expression of NKCC1 and WNK4 proteins were concurrently detected in the cortical neurons of hypertensive ischemic brains (Pearson's correlation, $r = 0.77$, $p < 0.003$). Interestingly, post-stroke administration of SPAK inhibitor ZT-1a in these hypertensive mice significantly reduced infarction and edema,

and improved neurological function recovery. **Conclusions:** Our study suggests that upregulation of WNK-SPAK-NKCC1 cascade in hypertensive ischemic brains may involve NF-κB transcriptional pathway, and contributes to the worsened outcome in hypertensive mice. Pharmacological inhibition of WNK-SPAK complex has therapeutic potential for stroke therapy with hypertension comorbidity. *This research was supported by VA Grant I01BX002891 (D. Sun).*

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Nanosymposium

448. Stroke I

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Presentation Number: 448.04

Topic: C.08. Ischemia

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Title: Inhibition of serum/glucocorticoid-regulated kinase 1 affords neuroprotection against cardiac arrest-induced brain injury

Authors: *M. S. GRAMES[1], C. Y.-C. WU[2], H. E. POSSOIT[2], G. A. CLEMONS[3], H. LIN[2], R. H.-C. LEE[2];
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Abstract: Cardiopulmonary arrest (CA) is the leading cause of death and disability in the United States. Cerebral blood flow (CBF) derangements are one of the major hallmarks of CA. Hypoperfusion (a decrease in CBF) following CA can persist for hours to days after ischemia and contributes to neuroinflammation, neuronal cell death and neurological deficits. Therefore, preventing hypoperfusion after CA can lead to more favorable neurological outcomes. Serum/glucocorticoid-regulated kinase 1 (SGK1), a serine/threonine kinase, plays a critical role for numerous cellular processes, including regulating homeostasis, inflammation, and apoptosis in various organs. However, the role of SGK1 in the brain is understudied. We previously discovered that SGK1 mRNA and protein expression in brain regions susceptible to ischemia (i.e. CA1 region of the hippocampus) were significantly elevated with hypoperfusion 24 hrs after

ACA. To explore the potential role of SGK1 in CA-induced hypoperfusion and brain injury, we inhibited SGK1 expression following CA using GSK 650394, a specific SGK1 inhibitor. A rat model of global cerebral ischemia (6 min asphyxia cardiac arrest, ACA) was used to induce CA. Intra-vital two-photon laser scanning microscopy and laser speckle contrast imaging revealed that pre-treatment with GSK 650394 (1.2 μg/kg, intracerebroventricular injection) immediately before ACA attenuated cortical hypoperfusion 24 hrs after ACA (32.40 ± 11.94% vs -0.66 ± 5.43%, respectively). Interestingly, neuroinflammation was reduced, while neuronal survival was enhanced in the CA1 region of the hippocampus after pre-treatment with GSK 650394. Finally, rats' functional learning and memory after ACA were evaluated using Y-maze and the novel object recognition test. Rats pre-treated with GSK 650394 exhibited better neurological outcomes following ACA as compared to untreated rats (0.61 ± 0.04 vs 0.45 ± 0.05, respectively). In conclusion, SGK is one of the major contributors to ACA-induced brain injury, while pre-treatment with GSK 650394 to reduce SGK1 expression provides neuroprotection against CA-induced hypoperfusion, neuroinflammation, neuronal cell death, and neurological deficits. Our study can lead to a novel therapeutic target for preventing brain injury following cerebral ischemia.

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Nanosymposium

448. Stroke I

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Title: Nadph oxidase drives formation of cofilin-actin rods during and after stroke

Authors: *S. WON[1], L. WU[2], J. WANG[2], J. R. BAMBURG[3], R. A. SWANSON[4];
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Abstract: Cofilin-actin rods are 1:1 assemblies of cofilin-1 and actin that can form in neuronal processes. These assemblies cause degeneration of neuronal processes in which they persist. Recent studies show that cofilin-actin rods form in neuronal dendrites and axons throughout regions of ischemia-reperfusion, and in the peri-ischemic zone of focal ischemic lesions. Interventions that suppress cofilin-actin rod formation thus have potential to improve outcome after stroke. Cofilin-actin rod formation is promoted by cofilin-1 de-phosphorylation, which in turn can be activated by oxidative stress. The studies presented here aimed to identify the pathways that are activated by ischemia and thus amenable to pharmacological intervention. Cell culture studies employed primary cortical mouse neurons at 10-13 days in vitro subjected to 30

minutes of “chemical oxygen-glucose deprivation (cOGD) to mimic stroke conditions. cOGD produced a robust, 2-3 fold increase in cofilin-actin rods. The increase began during cOGD, rose to a peak at 4 hours after cOGD, and then gradually declined over 24 hours. Rod formation was attenuated by the slingshot phosphatase inhibitor D3 and by the Rho II activator CN03, consistent with the previously identified role of cofilin de-phosphorylation in this process. Strikingly, the cOGD-induced formation of cofilin-actin rods was almost completely suppressed by pharmacological or genetic inhibition of neuronal NADPH oxidase (NOX2) or NMDA receptors, suggesting a key role for NMDA receptor mediated NOX2 activation in the signaling pathways controlling cofilin-1 phosphorylation state. We then evaluated cofilin-actin rod formation in the peri-infarct region of photothrombotic cortical stroke in the mouse. As in cell culture, D3 (10mg/kg) and CN03 (50 µg/kg) reduced rod formation, as did the NOX2 inhibitors apocynin and gp91ds-Tat. The cysteine pro-drug N-acetyl cysteine also reduced rod formation when administered after photothrombosis. These findings confirm the role of cofilin dephosphorylation in ischemia-induced rod formation, suggest that NOX2 - mediated superoxide production is upstream of cofilin dephosphorylation, and identify pharmacological agents that can be used to manipulate cofilin-actin rod formation in the setting of ischemic stroke.

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448. Stroke I

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Topic: C.08. Ischemia

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Title: Decoding the cross-talk between grafted neural stem cells and host brain to predict the molecular mechanisms of stem cells-induced functional recovery after stroke

Authors: *R. AZEVEDO-PEREIRA, N. C. MANLEY, C. DONG, J. VU, J. BERRY, G. SUN, T. BLISS, G. K. STEINBERG;
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Abstract: Human neural stem cell (hNSC) transplantation shows great potential as a therapy for ischemic stroke, yet little is known about the mechanisms by which hNSCs induce recovery. Elucidating the cross-talk between the grafted cells and the host brain is an important step towards identifying the molecular pathways driving hNSC-induced stroke recovery. A major challenge to this was distinguishing factors expressed by the graft from that of the host. We

overcame this critical barrier by adapting the novel TRAP (Translating Ribosome Affinity Purification) approach to separate graft and host mRNA. Using TRAP and RNAseq in combination with bioinformatic tools, we reliably distinguished hNSC graft and host transcriptomes following transplantation of hNSCs into the naïve or stroke-injured rat brain. To understand how transplanted hNSCs might influence the host brain we focused on hNSC genes encoding for secreted products; 386 secretome genes were identified. Gene ontology (GO) analysis identified biological processes occurring in the stroke-injured brain that could be affected by the graft secretome. These fell into 3 main categories: brain remodeling, immune response, and cilia. To predict which hNSC-secreted factors may drive stroke recovery we looked for graft secretome genes that were upregulated by the stroke microenvironment and also positively correlated with stroke recovery; 8 genes fit these criteria. NOG, which encodes for noggin, had the highest correlation with recovery and was the most differentially expressed gene with 6-fold higher expression in stroke versus naive rats. To determine how the stroke microenvironment may upregulate hNSC-expressed NOG, potential upstream regulators were identified using IPA. Seven candidates were predicted, of which Bmp2, Bmp6, Bmp7 and Tgfb1 were significantly upregulated in stroke tissue compared to naïve. *In vitro* testing revealed that all, except Tgfb1, increased NOG expression in hNSCs. Together these data predict that stroke upregulates BMP expression in the brain which in turn increases NOG expression in the grafted cells, and the graft-secreted noggin modulates various brain biological pathways to enhance stroke recovery. This approach paves the way to probe the molecular mechanisms of action of transplanted stem cells.

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Nanosymposium

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Title: Mechanisms of ischemia/reperfusion-induced type I interferon signaling in microglia

Authors: *A. MCDONOUGH[1], C. LEE[1], R. ARNOLD[1], R. V. LEE[1], J. R. WEINSTEIN[2]; [1]Univ. of Washington, Seattle, WA; [2]Neurol., Univ. Washington, Seattle, WA

Abstract: Ischemic and lipopolysaccharide (LPS) preconditioning are potent forms of neuroprotection against prolonged cerebral ischemia (stroke). Both ischemic preconditioning

(IPC) and LPS preconditioning are dependent on type I interferon (IFN) and Toll-like Receptor 4 (TLR4) signaling. Our investigations into the cellular and molecular mediators of preconditioning point to a critical role for these innate immune signaling pathways specifically in microglia, the resident immune cells of the brain. Our *in vitro* and *in vivo* models of IPC converge on a microglial type I IFN stimulated gene (ISG) response; studies from other groups suggest that type I IFN signaling is a shared downstream signaling pathway for preconditioning induced by multiple TLR agonists. Our *in vitro* model of exposing primary microglia cultures to hypoxia-hypoglycemia (ischemia/reperfusion-like conditions) suggests there is cross-talk between the TLR4 and IFNAR1 pathways via the signal transducer and activator of transcription 1 (STAT1) transcription factor. STAT1 is canonically specific to activation of IFNAR1 and becomes phosphorylated rapidly after microglia are treated with IFN-beta. Here we present data demonstrating that STAT1 is also phosphorylated in a time-dependent manner after microglia are exposed to LPS in a TLR4- and IFNAR1-dependent process. Furthermore, STAT1 phosphorylation occurs rapidly after exposure to hypoxia-hypoglycemia *in vitro* and this response is both TLR4- and IFNAR1-dependent. Our mechanistic studies demonstrate that stimulation with LPS, but not hypoxia-hypoglycemia, results in the release of type I IFNs from cultured microglia. Thus, we hypothesize that both intracellular and extracellular (autocrine/paracrine) mechanisms may be engaged to phosphorylate STAT1 and upregulate ISGs through either TLR4 or IFNAR1. Using *in vitro* exposure of STAT1-/- microglia to hypoxia-hypoglycemia and *in vivo* transient middle cerebral artery occlusion (tMCAO) in STAT1-/- mice, we demonstrate that the hallmark ISG feature in preconditioned microglia is lost and that STAT1 is a key regulator of the microglial response to a preconditioning stimulus.

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Nanosymposium

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Title: Resveratrol tretment reduces ischemic brain damage in reproductively senescent female rats

Authors: A. P. RAVAL[1], C. FURONES[2], W. ZHAO[3], K. DAVE[4], *M. A. PEREZ-PINZON[5]; [1]Neurol., [2]Peritz Scheinberg Cerebral Vascular Dis. Res. Laboratories, Dept. of Neurol., [3]Bioengineering, Univ. of Miami, Miami, FL; [4]Neurol., Univ. Miami Sch. Med., Miami, FL;

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Abstract: Cerebral ischemia (CI) is one of the leading causes of mortality and morbidity in the world, and strategies to prevent this disease or to mitigate its consequences are greatly needed. Studies from our laboratory demonstrated that resveratrol (RSV) - a natural polyphenol and an ischemic preconditioning mimetic-protects the brain from ischemic injury via activation of Sirt-1 in male rats/mice. It is well know that the brain exhibits many sex differences and women's risk and severity of ischemic damage increase exponentially after onset of menopause, and therefore the goal of the current study was to investigate the efficacy of RSV pre-/post-conditioning on innate immune response and ischemic outcome in reproductive senescence (RS) female rats. Since, inflammasome is a key component of the innate immune response after CI, we investigated inflammasome proteins viz.- NOD-like receptors (NLRs), ASC, caspase-1 after RSV treatment. We tested the efficacy of RSV using RS female rats that have been reproductively quiescent for months. RS rats were exposed to (transient middle cerebral artery occlusion (MCAO: 90 min) followed by randomly assigned to one of two treatment groups: Group 1-RSV (50 mg/kg), and Group 2-vehicle. RSV was administered 48h prior or 4.5 h after induction of MCAO. Twenty-four hours after MCAO, brains were removed rapidly and collected for western blotting or infarction area quantification. RSV treatment after MCAO significantly ($p<0.05$) reduced infarct volume in RS female rats as compared to vehicle treated group. Similarly, we also observed alterations in innate inflammatory markers in RSV treated group compared to vehicle treated group. Inflammasome components NLR and ASC require post-translational modification by phosphorylation and are currently being investigated. Results support that RSV treatment confers neuroprotection potentially via the Sirt1 signaling pathway in female rats, as we have observed previously in male rats.

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448. Stroke I

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Support: National Institute of Neurological Disorders and stroke Grant NS088084

Title: Peripherally impaired proteostasis aggravates ischemic stroke-caused neuronal injury in mice

Authors: *Y. LIU, K. SUBEDI, B. PAN, X. WANG, H. WANG;
Univ. of South Dakota, Vermillion, SD

Abstract: Impaired proteostasis has been linked to various diseases affecting both peripheral tissues and the brain. However, very little is known about the impact of impaired proteostasis in a peripheral tissue on ischemic stroke-induced brain injury. αB-Crystallin (CryAB) is known as a molecular chaperone that binds to and corrects intracellular misfolded/unfolded proteins to prevent non-specific protein aggregations. A missense mutation (R120G) in the CryAB gene ($CryAB^{R120G}$) causes proteinopathy in muscles, including the heart. To determine whether impaired proteostasis in a peripheral tissue influences brain injury and functional recovery following ischemic stroke, we functionally and pathologically studied the brain following ischemic stroke in the mice with cardiomyocyte-restricted overexpression of $CryAB^{R120G}$at 8 weeks of age when cardiac malfunction is not discernible. The $CryAB^{R120G}$ mice were subjected to the middle cerebral artery occlusion (MCAO) operation and then brain injury and functions were examined. Our results showed that there was increased infarct size and decreased neurologic function recovery after stroke in $CryAB^{R120G}$ mice compared with wild-type mice. Following stroke, Thioflavin S staining showed a large number of protein aggregates observed from the $CryAB^{R120G}$ mouse brains and Nissl staining revealed the reduced number of survival neurons in the $CryAB^{R120G}$ mouse brain. Additionally, a high level of activated astrocytes and microglia were found in the brain of $CryAB^{R120G}$ mice compared to those of wild-type mice following stroke. These results strongly suggest that peripherally impaired proteostasis aggravates ischemic stroke induced brain injury and neuroinflammation and disrupts brain functional recovery following ischemic stroke.

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Nanosymposium

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Title: Post-ischemic CaMKIIα ubiquitination reversibly inhibits CaMKII activity at the post-synaptic density by impairing CaMKIIα binding to ATP, calmodulin and substrates

Authors: C. POON, A. KAHL, I. BLANCO, V. PALFINI, R. RODNEY-SANDY, C. IADECOLA, ***K. HOCHRAINER**;
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Abstract: Calcium-calmodulin-dependent protein kinase II alpha (CaMKIIα) localizes to the post-synaptic density (PSD) where it promotes synaptic function by linking calcium signals to changes in synaptic strength and activity. CaMKIIα inactivation is linked to cerebral ischemic injury (Waxham 1996, Ashpole 2012), raising the possibility that re-establishing CaMKIIα activity could have potential as stroke therapy target. However, the molecular events that underlie CaMKIIα inactivation after ischemia are not known. Here we hypothesize that CaMKIIα inactivation at the PSD is caused by ubiquitination, a post-translational modification induced by cerebral ischemia-reperfusion (Hochrainer 2012, Liu 2004). Cerebral ischemia was induced in male C57BL6J mice by middle cerebral artery occlusion (MCAO) using an intravascular filament. Whole tissue extracts as well as cytosolic, synaptic membrane and PSD fractions were prepared at 1hr reperfusion to assess CaMKIIα ubiquitination, protein levels, enzymatic activity, binding to ATP, calmodulin and GluN2B. Removal of ubiquitin from CaMKIIα was achieved by incubation of lysates with recombinant USP2 deubiquitinase. MCAO induced CaMKIIα ubiquitination in the ischemic neocortex (159±4% of sham, 155±5% of contralateral, $P<0.001$, n=3/group) without affecting total CaMKIIα protein levels (98±1% of sham, $P=0.767$, n=3/group). CaMKIIα ubiquitination was particularly evident at the PSD (cytosol/membrane: 136±1%; PSD: 201±8% of sham, $P<0.001$, n=3/group), which coincided with severe suppression of PSD-associated CaMKII activity (31±6% of sham, $P<0.001$, n=9/group). CaMKII activity is strictly dependent on CaMKIIα binding to calmodulin (CaM) and ATP, as well as substrates. By nanoLC-MS/MS we localized the majority of post-stroke CaMKIIα ubiquitination sites to domains containing these binding sites. Coimmunoprecipitation studies showed a significant reduction of CaMKIIα interaction with CaM and ATP in the neocortical PSD fraction (CaM: 37±8%; ATP: 45±14% of contralateral, $P<0.01$, n=7-8/group). Association of CaMKIIα with the well-known PSD-localized phosphorylation target GluN2B was impaired as well (51±11% of contralateral, $P<0.01$, n=5/group). Deubiquitination restored CaMKIIα-CaM binding (95±4% of contralateral, $P<0.001$, n=4/group) and PSD-associated CaMKII activity (105.8±23% of sham, $P<0.001$, n=6/group), identifying ubiquitination as reversible repressor of CaMKII activity at the PSD. We conclude that CaMKIIα ubiquitination constitutes a previously unappreciated mechanism of post-ischemic CaMKII activity regulation that could open new avenues for the treatment of ischemic stroke.

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Title: Disruption of membrane trafficking leads to brain ischemia-reperfusion injury

Authors: D. YUAN[1], C. M. LOKE[1], C. LIU[1], *B. R. HU[2];
[1]Shock Trauma and Anesthsiology Res. Ctr., [2]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Neurons requires an extremely high level of membrane trafficking activities because of extraordinarily large surface area due to numerous axonal terminals and dendritic branches. For that reason, defects in the membrane trafficking pathway are a hallmark of all neurodegenerative disorders. A major cellular membrane trafficking pathway is the Golgi apparatus - late endosome - lysosome axis for supplying fast-turnover lysosomal enzymes. This pathway is regulated by N-ethylmaleimide sensitive factor (NSF) ATPase. This study shows evidence supporting a novel hypothesis that brain ischemia after cardiac arrest or stroke inactivates NSF ATPase, resulting in a cascade of events of disruption of the Golgi - endosome - lysosome pathway, release of cathepsin B (CTSB), and brain ischemia-reperfusion injury. This study demonstrates that active NSF is virtually totally depleted in neurons destined to die after brain ischemia. Consequently, Golgi, transport vesicles, and late endosomes are accumulated and damaged, which is followed by CTSB release from these damaged structures, resulting in ischemia-reperfusion brain injury. The hypothesis that CTSB release leads to ischemia-reperfusion brain injury is further supported by the fact that CTSB knockout mice have significantly smaller brain damage volume as well as significantly better long-term sensorimotor and cognitive functional recovery after brain ischemia in a mouse model of stroke.

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Title: Pharmacological calcium/calmodulin-dependent kinase (CaMKII) inhibition protects against Purkinje cell damage following CA/CPR in mice

Authors: N. CHALMERS[1], J. YONCHEK[1], K. BAYER[2], P. S. HERSON[3], ***N. QUILLINAN**[1]; [1]Anesthesiol., Univ. of Colorado, AMC, Aurora, CO; [2]Dept Pharmacol, Univ. of Colorado Denver, Aurora, CO; [3]Anesthesiol., UC Denver, Aurora, CO

Abstract: Objective: Ischemic brain damage is triggered by glutamate excitotoxicity resulting in neuronal cell death. Previous research has demonstrated that NMDA receptor activation triggers downstream calcium-dependent signaling pathways, specifically Ca^{2+}/calmodulin-dependent protein kinase 2 (CAMKII). Inhibiting CAMKII is protective against hippocampal ischemic injury, but there is little known about its role in the cerebellum. Here, we used pharmacological and genetic inhibition of CAMKII to assess it's role in Purkinje cell loss following global ischemia. **Methods**: To examine the neuroprotective potential of CAMKII inhibition in Purkinje cells we subjected C57BL/6 or CAMKIIα KO male mice (8-12 weeks old) to cardiac arrest followed by cardiopulmonary resuscitation (CA/CPR). We performed a dose-response study for tat-CN19o and cerebellar injury was analyzed at 7 days after CA/CPR. Acute signaling was assessed at 6 hours after CA/CPR using western blot analysis. **Results:** We observed increased phosphorylation of the T286 residue of CAMKII, suggesting increased autonomous activation. Analysis of Purkinje cell density revealed a decrease in cell density at 7 days after CA/CPR that was prevented with tat-CN19o at doses of 0.1 and 1 mg/kg. However, neuroprotection in the cerebellum required doses that were 10-fold higher than what was needed in the hippocampus (Deng, Cell Reports, 2017). CAMKIIα KO mice subjected to sham surgery or CA/CPR had similar Purkinje cell densities, suggesting CAMKIIα is required for CA/CPR induced injury in the cerebellum. We also observed a CA/CPR-induced activation of death associated protein kinase (DAPK1) that tat-CN19o did not block. **Conclusions:** CAMKII activation following CA/CPR is detrimental to Purkinje cells and inhibition of autonomous CAMKII activity is a promising therapeutic approach that is effective across multiple brain regions.

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Title: Post-translational modifications of alpha-synuclein play a role in ischemic brain damage

Authors: *T. KIM, S. L. MEHTA, A. K. CHOKKALLA, R. VEMUGANTI;
Neurolog. Surgery, Univ. of Wisconsin Madison, Madison, WI

Abstract: Transient cerebral ischemia is known to induce extensive post-translational modifications including phosphorylation and ubiquitination. We previously reported that alpha-synuclein (α-Syn), a Parkinson's disease-associated protein is acutely induced in the rodent brain after ischemic stroke and plays a detrimental role by mediating ischemic brain damage. Although shown in other neurodegenerative conditions, it remains to be elucidated whether α-Syn undergoes post-translational modifications that are associated with stroke disease outcome. Hence, we presently examined the effects of post-translational modifications on α-Syn in ischemic brain damage. Focal ischemia induced by transient middle cerebral artery occlusion (MCAO) significantly upregulated α-Syn protein expression and phosphorylation at S129 in the peri-infarct area of adult mice. Interestingly, both non-phosphorylated and phosphorylated α-Syn species translocated into the neuronal nuclei in the ischemic brain. PLK2 is known as the predominant kinase that phosphorylates α-Syn at S129. PLK2 knockout mice showed decreased infarct volume and improved motor function recovery after stroke. We also found that α-Syn is extensively ubiquitinated following cerebral ischemia, predominantly mediated by Nedd4 E3 ubiquitin-protein ligase. Deletion of Nedd4 in male mice decreased ubiquitinated α-Syn while increasing α-Syn protein levels, suggesting that Nedd4 promotes α-Syn degradation by the endosomal-lysosomal pathway. Functionally, Nedd4 knockout mice showed decreased infarct volume and ameliorated post-stroke motor deficits. Thus, our studies indicate that post-translational modifications on α-Syn following cerebral ischemia play a critical role in ischemic cell death.

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Title: NAD^+ precursor prevents post-ischemic increase in mitochondrial reactive oxygen species production via modulation of mitochondrial protein acetylation

Authors: *T. KRISTIAN[1,2], N. KLIMOVA[1], A. FEARNOW[2], A. LONG[2];
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Abstract: Global cerebral ischemia leads to increased production of reactive oxygen species (ROS) during the reperfusion period followed by DNA damage and overactivation of poly-ADP-ribose polymerase 1 (PARP1) with depletion of cellular NAD^+ pools. Post-ischemic NAD^+ levels can be replenished by the administration of nicotinamide mononucleotide (NMN), which serves as a precursor for NAD^+ synthesis. We have shown that NMN administration shows dramatic protection against ischemic brain damage and inhibits post-ischemic mitochondrial fragmentation. To shed more light on the mechanism of NMN-induced modulation of mitochondrial dynamics and neuroprotection we used our transgenic mouse models that express mitochondria targeted fluorescent protein in neurons and mice that carry knockout of mitochondrial NAD^+-dependent deacetylase sirt3 gene (SIRT3KO). Animals were subjected to transient global cerebral ischemia and at 2, 4 and 24 hours of recovery their brains were processed for biochemical and histological examination. The depletion of post-ischemic mitochondrial NAD^+ levels led to increase in mitochondrial protein acetylation, excessive mitochondrial fragmentation and high ROS generation. A single dose of NMN (about 60mg/kg) administered after the ischemic insult increased hippocampal mitochondria NAD^+ pools, normalized mitochondrial protein acetylation and post-ischemic ROS levels. The changes in mitochondrial protein acetylation were dependent on SIRT3 activity as confirmed by using SIRT3KO animals. Furthermore, ischemia caused an increase in mitochondrial superoxide dismutase (SOD2) acetylation, which was reversed by NMN treatment and dependent on SIRT3 activity. Thus, NMN treatment reduced SOD2 acetylation and resulted in a decrease in hippocampal reactive oxygen species (ROS) levels. Consequently, mitochondria in neurons become less fragmented due to reduced interaction of fission active phosphorylated dynamin-related protein 1 (pDrp1 (S616)), with mitochondria. In this work we identified a novel link between mitochondrial NAD^+ metabolism, post-ischemic ROS generation and mitochondrial dynamics, which can play a significant role in mechanisms of neuroprotection.

Disclosures: **T. Kristian:** None. **N. Klimova:** None. **A. Fearnow:** None. **A. Long:** None.

Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

Location: Room N227

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 449.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant RO1 NS109090-01

Title: Magnetic resonance imaging quantification of hemorrhage predicts acute motor function after cervical spinal cord injury in the rat

Authors: *S.-Y. LEE[1], N. WILKINS[2], S. N. KURPAD[2], B. D. SCHMIT[3], M. D. BUDDE[2]; [1]Biophysics, [2]Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI; [3]Dept. of Biomed. Engin., Marquette Univ. Dept. of Biomed. Engin., Milwaukee, WI

Abstract: Intramedullary hemorrhage following traumatic spinal cord injury is consistently identified as an MRI feature associated with poorer neurological outcomes. The presence of hemorrhage is predictive of complete lesion, and it is associated with the most severe neurological deficit. However, imaging guided therapeutic strategies for hemorrhagic injury are limited. As a first step to develop therapeutic strategies, the study aims to investigate the relationship between quantity metrics derived from MRI and neurological outcomes in a rat cervical contusion model. Ten female Sprague-Dawley rats received hemi-contusion injury at C5 by a 10g weight dropped from 25 mm to induce moderate SCI. The rats underwent MRI at 1 day post injury (dpi). T_2- and T_2*- weighted images were used to quantitatively assess edema and hemorrhage, respectively, using several morphological parameters: maximal length and maximal area on sagittal and axial slices. Diffusion tensor imaging, and double diffusion encoded MRI were used to quantify microscopic injury. Motor and sensory functions were evaluated at 2 dpi using forelimb locomotor assessment scale (FLAS), modified Basso, Beattie and Brasnahan (mBBB) scoring, grooming test, Von Frey test, and hot plate test. Hemi-contusion injury at C5 impaired ipsilateral limbs, especially in the forepaw. T_2-weighted and T_2*-weighted image clearly showed edema and hemorrhage which was primarily localized to the gray matter. Unlike prior studies in the thoracic spinal cord contusion, the injury was not strongly evident on diffusion maps ($fADC_{||}$, FA, and AD). Ipsilateral motor function was strongly related to the quantitative measures of hemorrhage ($R^2 = 0.78$, $p = 0.008$) and edema ($R^2 = 0.72$, $p = 0.002$), but no associations were evident with sensory function. DWI metrics were not strongly correlated with neurological functions. These results in a rat cervical model support prior human studies of showing greater neurological function with more extensive hemorrhage. The results differ from prior studies in the thoracic spinal cord injury in which hemorrhage was not a strong indicator of dysfunction while DWI was predictive of injury severities. The likely interpretation is that the localization of injury to the gray matter in the cervical hemi-contusion model both limits the sensitivity of DWI and results in predominantly ipsilateral forepaw dysfunction. The strong association between hemorrhage and neurological dysfunction in this model further supports the role of MRI in evaluation of preclinical therapies and furthers the notion that hemorrhage may be a therapeutic target through surgical or hemostatic approaches in spinal cord injury.

Disclosures: S. Lee: None. **M.D. Budde:** None. **S.N. Kurpad:** None. **B.D. Schmit:** None. **N. Wilkins:** None.

Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

Location: Room N227

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 449.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation (# 546401) to LMC
Department of Defense (SC150225) to LMC

Title: Spinal contusion injury-induced ejaculatory dysfunction is reduced by intrathecal infusions of gastrin releasing peptide in male rats

Authors: *S. GAIKWAD[1], N. KOZYREV[2], L. M. COOLEN[3];
[1]Univ. of Mississippi Med. Ctr., Jackson, MS; [2]Robarts Res. Inst., London, ON, Canada; [3]Biol. Sci., Kent State Univ., Kent, OH

Abstract: Spinal cord injury (SCI) has devastating effects on urogenital functions, including severe deficits in ejaculation. Surveys among SCI men place recovery of sexual function as a high priority issue, but treatment development is hindered by limited understanding of effects of SCI on the spinal ejaculation generator (SEG). The SEG consists of a population of lumbar spinothalamic cells (LSt) that control ejaculation via axonal projections to autonomic and motor centers in the lumbosacral spinal cord. LSt cells control ejaculation via release of neuropeptides, notably gastrin releasing peptide (GRP). In control male rats, intrathecal infusions of GRP strongly facilitate ejaculatory reflexes, while GRP antagonists prevent ejaculation triggered by stimulation of the dorsal penile nerve (DPN). We have recently demonstrated that SCI completely ablated DPN-induced ejaculatory reflexes in male rats. Moreover, ejaculatory dysfunction was associated with significantly reduced expression of *GRP* mRNA and protein in LSt cells. Here, we test the hypothesis that GRP infusions may restore ejaculatory reflexes in SCI males. In a first study, male Sprague Dawley rats received either controlled spinal contusion at 200 Kdynes (n=8) or sham treatment (n=8). Four weeks later, animals received an acute spinal transection to remove remaining supraspinal influence on the SEG and subsequent intrathecal infusions (10 µl) of saline and GRP 20-29 (0.2 nmol) while parameters of ejaculatory reflexes were recorded. In addition, DPN was stimulated at frequencies that normally trigger ejaculation in control males (30 Hz) or subthreshold (5 Hz) and reflexes were recorded. GRP, but not saline triggered ejaculatory reflexes and facilitated DPN-stimulated reflexes equally in sham and SCI groups. In a second study, the procedures were repeated, but without the acute spinal transection prior to infusions. Again, GRP, but not saline, triggered and facilitated ejaculatory reflexes with no differences between sham and SCI groups. These results indicate that a reduction of GRP in LST cells following SCI may contribute to ejaculatory dysfunction. Moreover, GRP may be a target for development of treatment options for sexual dysfunction following SCI.

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Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

Location: Room N227

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Presentation Number: 449.03

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH T-32-NS076401
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Title: Cellular basis of dectin-1/Clec7a mediated axon regeneration

Authors: *L. D. HUFFMAN[1], R. PASSINO[2], P. DUNCKER[3], B. SEGAL[4], R. GIGER[2];
[1]Neurosci., [2]Cell and Developmental Biol., [4]Neurol., [3]Univ. of Michigan, Ann Arbor, MI

Abstract: Severe nervous system insults including spinal cord injury, stroke, and traumatic brain injury affect hundreds of thousands of individuals and often inflicts deep cutting physical, mental, and psychological damage. Many treatment avenues have been pursued to protect the nervous system from further damage and while these efforts may prove effective in staving off secondary injury, the major outstanding goal is to induce regenerative growth of injured neurons or induce compensatory sprouting of nearby neurons. One mechanism to influence the neuronal response to injury is through manipulation of the immune system. This study proposes to examine the cell-types and molecular players involved in immune-mediated neurorepair. In recent years, several damage-associated molecular pattern receptors, including toll-like receptor 2 (TLR2) and **dectin-1/Clec7a**, have shown importance in promoting axonal regeneration of retinal ganglion cells (RGCs) in the injured adult mouse optic nerve. Activation of these receptors with compounds like the yeast cell wall extract **zymosan, β-glucan,** or **Pam3Cys,** enhances regeneration of RGCs following optic nerve crush injury and has also shown promise in models of spinal cord injury. Previously in our lab, we have investigated which immune infiltrates are present following injection of zymosan or β-glucan into the posterior chamber of the mouse eye. Further work showed that in *dectin-1* null mice, the pro-regenerative effects of zymosan are greatly reduced. A key open question concerns the immune cell types and molecules associated with zymosan/dectin-1 mediated neurorepair. To address these questions, we generated *dectin-1(flox/flox)* mice that allow conditional gene ablation. When crossed with *LysM-cre* mice, we observe a 30% reduction in dectin-1 in monocytes and a near complete loss in neutrophils, as assessed by flow cytometry. Conditional gene ablation studies are complemented by parabiosis experiments in which wildtype and dectin-$1^{-/-}$ mice share the same circulatory system. Together these experiments are expected to reveal in which immune cells dectin-1 function is required for zymosan-elicited RGC axon regeneration.

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Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Grafted human embryonic stem cell derived astroglia can repair the injured spinal cord

Authors: *Y. LIU[1], Y. SUN[1], P. JIANG[2], W. DENG[3];
[1]Inst. of Neurosci., Soochow Univ., Suzhou, China; [2]Rutgers Univ., Piscataway, NJ; [3]Univ. of California, Davis, Davis, CA

Abstract: For this study, we transplanted human embryonic stem cell-derived astroglia (NPC- and Olig2PC-Astros) into lesioned spinal cords of mice to test the cells' ability to promote spinal cord healing. The grafted astroglia survived in the lesion and migrated into the rostral and caudal spinal cord regions. The grafted astroglia assisted healing by reducing scar formation, protecting lesion-area neurons, and promoting regrowth of descending serotonergic and corticospinal axons. Re-formed synapses were detected between sprouting serotonergic axons and motor neurons, glutamatergic neurons, and GABAergic interneurons caudal to the lesion site. These positive effects resulted in slightly increased Basso Mouse Scale scores and electrophysiological transmission between the lesioned spinal cord and hind limbs compared with vehicle-treated control animals. Proteomic expression profiles of the injured spinal cords treated with the astroglia showed that the subtypes improved the injuries to different extents. These astroglia, especially the NPC-Astros, hold promise for treatment of spinal cord injuries.

Disclosures: Y. Liu: None. **Y. Sun:** None. **P. Jiang:** None. **W. Deng:** None.

Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

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Presentation Number: 449.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Insight Institute of Neurosurgery and Neuroscience

Title: A novel electromagnatic-neurobiologic interface for functional animation of dormant motor nerve roots in spinal cord injury via neuromodulation

Authors: *J. SHAH[1,2,3,4], A. AL-GHARAIBEH[2,3], R. SMITH[2];
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Abstract: Complete spinal cord injury (SCI) is a devastating occurrence afflicting millions of people worldwide with no available treatment for functional motor recovery. Recently, epidural electrical stimulation has shown therapeutic potential in incomplete SCI. However, the lack of effect in complete SCI raises the necessity to test alternative approaches. In this study, we describe surgical procedure that provides a neuromodulation of motor nerve roots in a case with complete motor and sensory paraplegia. We used a novel retrograde intraforaminal approach and placed multiple electrodes from L2 to S1 along the nerve roots of a T5 traumatic paraplegic patient who was diagnosed with complete motor and sensory paraplegia; T5 ASIA, grade A. By connecting to battery power and using computer algorithms to modulate individual nerve roots, precise and synchronous movements were achieved. First week after the implantation, the patient was able to move lower limbs at different joints in a precise manner with stimulation. Intensive physical therapy sessions were followed and showed increases in muscle strength and bulk. Moreover, the patient was able to stand with stimulation for a maximum of 54 seconds within the first month of rehabilitation. Our case demonstrates the ability to modulate motor nerve roots in precise, replicable and targeted manner. Our approach shows a therapeutic potential in complete SCI with the possibility of a parallel electric circuitry that can effectively bridge a damaged spinal cord, and lead to functional recovery when combined with rehabilitation programs.

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Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: New myokine-mediated improvement of motor function and muscle atrophy in chronic spinal cord injury

Authors: *C. TOHDA, A. KODANI, T. KIKUCHI;
Div. of Neuromedical Sci., Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan

Abstract: Chronic spinal cord injury (SCI) is difficult to cure, even by several approaches effective at the acute or subacute phase. Although the majority of SCI studies have focused on the nervous system and inflammatory cells in the spinal cord, we targeted skeletal muscle atrophy, as a characteristic finding in the chronic phase. Because, a longitudinal study showed that skeletal muscle atrophy progresses in a manner dependent on the time after injury in humans. Disuse of skeletal muscle and loss of motor neurons synergistically induce muscle atrophy. On the contrary, exercise was shown to slightly improve motor function when applied during the chronic phase. Although skeletal muscle secretes myokines responded to muscle activity, we considered that some myokines might regulate neural function. Thus, we hypothesized that stimulation of skeletal muscle with drugs rather than exercise might activate the release of known or yet unknown myokines, with the notion that the identification of such drugs and new myokines would pave a new way of therapy for SCI.We explored drugs that protect against muscle atrophy and activate secretion of axonal growth factors from skeletal muscle, and found that acteoside induced the secretion of axonal growth factors from skeletal muscle cells and proliferation of these cells. Intramuscular injection of acteoside in mice with chronic SCI recovered skeletal muscle weight reduction and motor function impairment. We also identified pyruvate kinase isoform M2 (PKM2) as a secreted factor from skeletal muscle cells, stimulated by acteoside. Extracellular PKM2 enhanced proliferation of skeletal muscle cells and axonal growth in cultured neurons. Further, we showed that PKM2 might cross the blood-brain barrier. These results indicate that effects of acteoside on chronic SCI might be mediated by PKM2 secretion from skeletal muscles. This study proposes that the candidate drug acteoside and a new myokine, PKM2, could be used for the treatment of chronic SCI.

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Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

Location: Room N227

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 449.07

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Cigarette smoke dose-dependently exacerbates clinical symptoms and pathology in a mouse model of multiple sclerosis

Authors: *K. KOSHIBU[1], J. HO[2], W. XIA[2], A. KONDYLIS[1], L. GARCIA[1], K. LUETTICH[1], B. PHILLIPS[1], J. HOENG[1], M. PEITSCH[1];
[1]PMI R&D, Philip Morris Products S.A., Neuchatel, Switzerland; [2]PMI R&D, Philip Morris Intl. Res. Labs. Pte. Ltd., Singapore, Singapore

Abstract: Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system. The etiology of the disease is complex and involves an interplay between genetic and environmental factors. Cigarette smoke (CS) has emerged as a major risk factor associated with the onset of MS. To further address this topic, we studied the effect of chronic CS exposure using an experimental autoimmune encephalomyelitis (EAE) model of MS in mice. Among several models of human MS, EAE is the most commonly applied animal model for investigating the pathogenesis of and discovering therapeutic interventions for MS. A substantial number of drugs available on the market have demonstrated concordant results in both EAE and MS, suggesting a predictive value of EAE as a pre-clinical model for human MS. In our study, we chose a myelin oligodendrocyte glycoprotein (MOG) amino acid 35-55-induced EAE mouse model to investigate the effect of three doses of CS exposure over six weeks on EAE onset, progression, severity, incidence, and spinal cord pathology. Interestingly, we discovered that CS can differentially affect clinical symptoms and spinal cord lesions in a dose-dependent manner. Low and medium doses exacerbated the severity of the symptoms, while the high dose had no effect. The spinal cord pathology largely paralleled these observations. In conclusion, the results partially confirmed the observations found in humans that CS can worsen EAE symptoms and pathology when mice are exposed to specific doses of CS before and after the induction of EAE.

Disclosures: **K. Koshibu:** A. Employment/Salary (full or part-time):; PMI (full time). **J. Ho:** A. Employment/Salary (full or part-time):; PMI (full time). **W. Xia:** A. Employment/Salary (full or part-time):; PMI (full time). **A. Kondylis:** A. Employment/Salary (full or part-time):; PMI (full time). **L. Garcia:** A. Employment/Salary (full or part-time):; PMI (full time). **K. Luettich:** A. Employment/Salary (full or part-time):; PMI (full time). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PMI, Vertex Pharmaceuticals. **B. Phillips:** A. Employment/Salary (full or part-time):; PMI (full time). **J. Hoeng:** A. Employment/Salary (full or part-time):; PMI (full time). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PMI. **M. Peitsch:** A. Employment/Salary (full or part-time):; PMI (full time). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PMI.

Nanosymposium

449. Spinal Cord Injury: Models, Mechanisms, and Therapeutic Strategies

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation
American Association of Immunologists
Cotswold Foundation

Title: Inhibiting central sTNF during chronic spinal cord injury improves antiviral immunity

Authors: *D. M. NORDEN[1], J. JIANG[1], J. RICARD[1], **V. BRACCHI-RICARD**[1], V. J. TOM[2], J. R. BETHEA[1];
[1]Biol., Drexel Univ., Philadelphia, PA; [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Injury to the spinal cord leads to compromised neuro-immune communication and deficits in antiviral immunity. Previously, we reported increased mortality and prolonged viral clearance in mice with chronic spinal cord injury (SCI) infected with influenza virus. The reason for impaired immune function following SCI remains unknown, but may be related to heightened levels of inflammation within the injured spinal cord. SCI-induced neuroinflammation is detrimental to homeostatic neuronal functions and is thought to be an underlying factor in pathological outcome, aberrant plasticity, and hyperexcitable circuits. The pro-inflammatory, soluble form of tumor necrosis factor (sTNF) is elevated chronically within the spinal cord following SCI and is associated with various forms of plasticity that could increase neuronal excitability. Therefore, we began investigating whether inhibiting SCI-induced sTNF with XPro1595, a biologic that disrupts sTNF signaling, would attenuate SCI-induced plasticity, immune dysfunction, and improve antiviral immunity in chronically injured mice. Mice received mid-thoracic (T9) contusion injury and XPro was infused to the spinal cord via osmotic minipumps for 4 weeks, at which time mice were challenged with X31 influenza virus. Following virus infection, SCI-saline mice lost a significant amount of weight relative to SCI-XPro and non-injured mice. In fact, SCI-XPro infected and non-injured infected mice had identical weight loss curves. Tetramer assays demonstrated that SCI-XPro infected and non-injured infected mice had significantly more virus-specific CD8 T cells in the lung and spleen compared to SCI-saline infected mice. Finally, SCI XPro infected and non-injured infected mice had significantly lower viral NP mRNA levels in their lungs compared to SCI-saline treated mice. Moreover, inhibiting systemic sTNF after injury did not improve antiviral immunity. These results demonstrate that central sTNF inhibition by XPro can restore the impaired virus-specific CD8 T cell response in peripheral organs and significantly improve recovery from virus infection in chronic SCI mice. Current mechanistic studies are investigating how sTNF signaling within the spinal cord impacts immune function.

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Nanosymposium

450. Cerebellum Circuits and Functions

Location: Room N426

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 450.01

Topic: E.02. Cerebellum

Support: NIH Grant NS105155

Title: Investigating the synaptic and circuit mechanisms of essential tremor using a novel mouse model

Authors: *M. ZHOU[1], M. D. MELIN[1], W. XU[2], T. C. SUDHOF[1];
[1]Mol. and Cell. Physiol., Stanford Univ., Stanford, CA; [2]Neurosci., UT Southwestern, Dallas, TX

Abstract: Essential tremor (ET) is one of the most common neurological disorders. It is characterized by an action tremor that most commonly affects arms but also other body parts, impacting 0.3-5.6% in the general population. Despite its high prevalence, the underlying neural mechanisms of ET are poorly understood, and as a result, current medications and surgical treatments are of limited effectiveness. In this study, we generated a novel genetic mouse ET model and investigated the synaptic and circuit mechanisms underlying ET. We found that homozygous synaptotagmin 2 conditional knockout mice crossed with parvalbumin-Cre positive mice exhibit similar behaviors as ET human patients. Combining mouse genetics, mouse behaviors, viral manipulation, circuit tracing and slice recording techniques, we identified the specific brain region, cell type, brain pathway and synaptic release defects underlying ET. These results will not only provide insights into the etiology of ET, but also shed lights into the therapeutic interventions of this common disease.

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Nanosymposium

450. Cerebellum Circuits and Functions

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Presentation Number: 450.02

Topic: E.02. Cerebellum

Support: NINDS/NIA NS075321
American Parkinson Disease Association
NINDS RO1 NS41509

Greater St. Louis Chapter of the American Parkinson Disease Association
Barnes Jewish Hospital Foundation (Elliot Stein Family Fund)
NIH T32 GM007356
Wilbur Smith Pediatric Neurology Fund

Title: Functional connectivity reveals large-scale network dysfunction in essential tremor

Authors: *A. E. MORRIS[1], S. A. NORRIS[2], J. W. MINK[1], J. S. PERLMUTTER[2]; [1]Neurol., Univ. of Rochester Med. Ctr., Rochester, NY; [2]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Essential tremor (ET) is the most common movement disorder in adults, yet its pathophysiology is poorly understood. Neuroimaging evidence implicates cerebello-thalamo-cortical pathways in the mechanism of ET, but many of these studies were collected during task-activation states while participants manifested tremor and thus may reflect brain responses to the unwanted movements rather than primary pathophysiology. Using resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) to study brain circuitry limits movement-related confounds. We recruited patients with ET from the Washington University Movement Disorders Center. Each subject had resting-state scans (3 BOLD 7.3 min runs) with eyes closed and were observed for movement during scan acquisition. Tremor rating scale severity was assessed pre- and post-operatively at optimal DBS settings. Age and sex-matched healthy control (HC) data were obtained from scans previously collected by the lab. Rigorous preprocessing was performed to minimize the effect of head motion during scan acquisition. 300 seed regions were applied across the cortex, cerebellum, basal ganglia and thalamus to comprehensively sample the whole brain. Subject connectomes were obtained by computing the correlation between seed average time courses for each seed pair. Group-level differences were assessed using weighted object-oriented data analysis, a novel statistical method for comparisons of whole connectome objects. We next used composite FC scores, i.e. mean cross-correlation between nodes, to assess functional connectivity (FC) at the network-level. Finally, we assessed regional FC by computing a seed correlation map between a motor thalamus seed and all voxels in the brain. Significant group differences were assessed on a cluster-wise basis.We obtained rs-fcMRI scans in 21 volunteers with ET and 34 HC participants. Patients with ET have large-scale differences in connectome structure. Post-hoc tests of select network-level FC revealed decreased overall thalamo-somatomotor, thalamo-visual and auditory-visual FC in ET versus HC. Network FC measures did not correlate with clinical tremor measures. Motor thalamus FC was significantly increased with primary motor cortex and decreased with occipito-parietal and cerebellar regions in ET versus HC. These results demonstrate aberrant connectome, network and regional FC and further implicate cerebello-thalamo-motor pathway dysfunction in ET. Remarkably, thalamic and visual networks had the greatest FC differences while cerebellar effects were much smaller. These results may reflect asynchrony of visual feedback and motor systems in ET.

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Nanosymposium

450. Cerebellum Circuits and Functions

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Presentation Number: 450.03

Topic: E.02. Cerebellum

Support: MOST 106-2410-H-010-004-MY2
MOST 108-2420-H-010-001

Title: Cerebellar rTMS modulates the performance of procedural learning task: A TMS-MRS study

Authors: *Y. LIEN, S.-H. LIN, C.-P. LIN, L.-H. CHANG;
Inst. of Neurosci., Natl. Yang-Ming Univ., Taipei City, Taiwan

Abstract: Could cerebellar modulations influence our processing of learning? Research has shown that the cerebellum is not only related to motor processing but is also actively involved in several cognitive skill acquisitions; however, it is still not clear how the cerebellum and its associated cerebro-cerebellar circuits contribute to those cognitive functions. In order to answer this question, we investigated the modulations of frequency-dependent cerebellar repetitive transcranial magnetic stimulation (rTMS) with a procedural learning task and measured participants' neurochemical status via MR spectroscopy (MRS) techniques.
We first applied standard pursuit rotor task training to observe the processing of procedural learning and its associated visuomotor coordination functions. In order to quantify the metabolic signals associated with the behavior performance, we obtained baseline MRI and MRS scans to guide our region-of-interest in the cerebellar vermis area and measured the regional GABA and Glutamate-Glutamine (Glx) concentrations. Healthy participants (N=43) were randomly assigned to TMS high frequency (HF, 10Hz), low frequency (LF, 1Hz), and sham groups with the rTMS interventions.
Our results demonstrated that the improvement of procedural learning ability in the HF group was significantly larger than in the other groups (HF vs LF: $p < 0.001$, HF vs sham: $p < 0.01$). On the other hand, the index of cortical excitability from visual and motor areas through the visual phosphene threshold and motor threshold measures did not experience any significant change, suggesting that procedural learning benefits may come from the cerebro-cerebellar associated network rather than intrinsic changes among the visual and motor cortex. Our results also indicated that the ratio of the Glx and GABA neurotransmitters was significantly correlated with behavioral improvement during procedural learning (sham, $p<0.05$). These findings suggest that cerebellar rTMS could modulate the procedural learning performance in a frequency-dependent manner; furthermore, the behavioral efficacy of rTMS was associated with the GABA and Glx neurochemical balance in the cerebellum. Hence, these results suggest that cerebellar rTMS may influence metabolic concentrations and be related to the efficacy of learning and cognitive skill acquisition.

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Nanosymposium

450. Cerebellum Circuits and Functions

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Topic: E.02. Cerebellum

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CAUT19AFP003

Title: Evolving cerebellar neural representations during learning of an evidence-accumulation decision-making task

Authors: ***M. OOSTLAND**, B. DEVERETT, S. S.-H. WANG;
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: To make decisions based on sensory evidence, it is necessary to create and manipulate representations of this evidence in memory, then act upon an evaluation of the evidence. Previously (Deverett et al., 2018 eLife; Deverett et al., bioarXiv) we showed that Purkinje cells of the lateral posterior cerebellum (crus I) express neural correlates of evidence, memory, and choice in a decision-making task for head-fixed mice, and that disruption of this activity shortens the timescale of memory and reduces the accuracy of decisions. Next we want to understand how these neuronal representations are represented and transformed in the deep cerebellar nuclei. We used multi-channel silicon probes (Neuronexus and Neuropixels) to record from crus I and the dentate nucleus throughout the learning process. In trained mice, cells in the dentate nucleus show a transient increase in firing rate in response to individual cues. Throughout the cue period, a subset of cells in the dentate nucleus increase their firing rate, similar to the responses of Purkinje cells in Crus I during the cue period. Next, we aim to study how these neuronal representations of sensory evidence change over time while mice are learning the evidence-accumulation decision-making task. The results can help to understand the role of cerebellar processing in shaping the accuracy of accumulated evidence.

Disclosures: **M. Oostland:** None. **B. Deverett:** None. **S.S. Wang:** None.

Nanosymposium

450. Cerebellum Circuits and Functions

Location: Room N426

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 450.05

Topic: E.02. Cerebellum

Support: RO1 NS096289, CAH

Title: Evaluating pattern separation in the cerebellar granule cell layer

Authors: *E. FLEMING, C. HULL;
Duke Univ., Durham, NC

Abstract: Linking experience and movement is fundamental to all animals, especially the ability to predict that context warrants a motor response. Such associations often rely on the cerebellum, a structure critical for motor learning. The cerebellum harnesses sensory, motor, and cognitive information (i.e. context) from afferent projections that converge on a dense layer of granule cells. Large-scale divergence onto granule cells, in combination with sparsening of activity through broad inhibition, is thought to create unique representations that can be learned by downstream Purkinje cells, the sole output neurons of the cerebellar cortex (Marr, 1969; Albus, 1971). However, recent studies have challenged classical models by showing that granule cell population responses can be dense and redundant when stimuli are delivered during some behaviors (Giovannucci et al, 2017; Knogler et al, 2017). These findings call into question how the granule cell layer generates the computational complexity to represent the multitude of unique input patterns the cerebellum learns to associate with motor output. By delivering sensory input outside the context of a behavioral task in awake mice, and parametrically varying stimulus features while controlling for movement-related activity, I have tested how granule cells encode unique stimulus representations and how multiple stimuli are integrated at the population level. Using video-rate calcium imaging, I have found that sensory representations are sparse, encoded by < 5% of the population. The identity of unimodal sensory stimuli are represented by largely non-overlapping granule cell ensembles. Moreover, by varying stimulus intensity I find that population responses can be thresholded, with high intensities producing reduced population responses compared to moderate stimulus intensities. Finally, by delivering multiple stimuli simultaneously or in close temporal proximity, I find that the granule cell layer performs subtractive, as well as additive, integration in a stimulus-specific manner. These results suggest a role for local inhibition in shaping stimulus representations through gain control and spike thresholding that can be global or stimulus-specific. To test the role of local inhibition in shaping granule cell responses, I am performing acute, cell-type specific manipulations of granule cell GABAergic inhibition during sensory input. These experiments suggest that sparsity and stimulus-specific recruitment of inhibition support pattern separation in the cerebellar granule cell layer.

Disclosures: E. Fleming: None. **C. Hull:** None.

Nanosymposium

450. Cerebellum Circuits and Functions

Location: Room N426

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 450.06

Topic: E.02. Cerebellum

Support: NIH Grant DC012775

Title: Purkinje cells regulate motor coordination in developing zebrafish

Authors: *D. E. EHRLICH[1], D. SCHOPPIK[2];
[1]Neurosci. Inst., NYU Langone Med. Ctr., New York, NY; [2]Neurosci. Inst., New York Univ., New York, NY

Abstract: Mature locomotion requires that animal nervous systems coordinate distinct groups of muscles. The pressures that guide the development of coordination are not well understood. We studied vertical locomotion in developing zebrafish to understand how and why coordination might emerge. We found that zebrafish used their pectoral fins and bodies synergistically to climb. As larvae developed, they changed the way they coordinated fin and body movements to climb with increasingly stable postures. Fin-body synergies were absent in mutants without vestibular sensation, linking sensed imbalance to coordinated movements. Similarly, synergies were systematically altered following lesions of cerebellar Purkinje cells, identifying a neural substrate regulating fin-body coordination. Computational modeling extended our behavioral findings, illuminating trade-offs involved in improved balance as zebrafish mature. Together these findings link balance to the maturation of coordinated locomotion. Developing zebrafish improve postural stability by optimizing fin-body coordination. We therefore propose that the need to balance drives the development of coordinated locomotion.

Disclosures: D.E. Ehrlich: None. **D. Schoppik:** None.

Nanosymposium

450. Cerebellum Circuits and Functions

Location: Room N426

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 450.07

Topic: E.02. Cerebellum

Support: KAKENHI 19K06756

Narishige Fund
The Kao Foundation for Arts and Sciences

Title: Identifying functional compartments in the developing cerebellum: Calcium and voltage imaging in zebrafish

Authors: K. HIYOSHI, N. FUKUDA, K. OKUMURA, K. YAMSU, ***S. TSUDA**;
Saitama Univ., Saitama, Japan

Abstract: During cerebellar development, a multitude of neurons are generated and form functional circuits. For a deeper understanding of cerebellar function, it is important to uncover the organizing principles as well as the development of such functional circuitry. To address this issue, especially focusing on cerebellar compartments, which is suggested to work as functional modules in the cerebellum, we have applied optical approaches and behavior analysis to zebrafish, an ideal model system for studying neurogenesis and optical techniques. First, to determine functional compartments in the developing cerebellum, we performed optokinetic response (OKR) test, while observing Purkinje cell activity by whole-cerebellum and high-speed calcium imaging. For this, we used transgenic fish which express GCaMP6s specifically in Purkinje cells. At 6 day post fertilization, when stable OKR was observed, specific populations of Purkinje cells were activated during OKR, and their distribution pattern was different depending on the direction of visual stimuli. By conducting spatiotemporal analysis and 3D-reconstruction of the recorded Purkinje cells at single-cell resolution, we obtained 3D maps of all the recorded Purkinje cells. Four groups of Purkinje cells were found to show distinct patterns of activity, forming clusters in a 3D manner. Furthermore, to examine functional circuits in the developing cerebellum in more detail, we applied genetically encoded voltage indicators (GEVIs), ASAP1, QuasAr2, and Arclight, to zebrafish. By using Gal4-UAS system, we succeeded in recording the spontaneous activity of spinal cord neurons at single-cell resolution as well as the evoked depolarization and hyperpolarization in the cerebellum with ASAP1 and Arclight. These findings obtained by our comprehensive and spatiotemporal analysis of Purkinje cell activity illuminate the structure and roles of functional compartments in the developing cerebellum, which would help understand the emergence of the cerebellar compartments.

Disclosures: K. Hiyoshi: None. **N. Fukuda:** None. **K. Okumura:** None. **K. Yamsu:** None. **S. Tsuda:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.01

Topic: F.04. Stress and the Brain

Support: R01-AA026844
R01-AA013892
K08-AA023545

Title: Stress, pain, and hyperactive limbic response in individuals with trauma

Authors: *D. SEO[1], R. DOUGLAS[1], C. LARKIN[1], S. HWANG[1], C. LACADIE[2], R. SINHA[1]; [1]Psychiatry, [2]Radiology, Yale Sch. of Med., New Haven, CT

Abstract: Repeated stress and adversities increase risk for morbidity by inducing high allostatic load that disrupts mental and physical homeostasis. A link between cumulative stress and physical disruption was previously found in healthy individuals including adverse health symptoms associated with hypoactive ventromedial prefrontal cortex (VmPFC) and hyperactive limbic response to stress. However, a specific neural link in individuals with clinical disorders remains unclear. The present study investigated neural correlates of stress, trauma, and pain using functional magnetic resonance imaging (fMRI). Participants were 10 individuals with trauma (TR: 9 women) and 18 healthy controls (HC: 16 women) with no demographic difference (age, M=26.36; SD=7.3). The status of trauma was determined based on the criteria for posttraumatic stress disorder using the Diagnostic and Statistical Manual of Mental Disorder (DSM-5). fMRI response was examined during exposure to stress and neutral-relaxing pictures. To understand the associations between stress and health related symptoms in a real-life setting, all participants were followed daily for 30 days using a smartphone app. Neuroimaging results indicated altered VmPFC-limbic response and increased negative emotion after viewing stressful pictures in TR relative to HC ($t=2.3$, $p<0.05$). During stress, TR showed hypoactivity in the VmPFC, but hyperactivity in limbic-striatal regions including the amygdala, hippocampus, striatum and insula ($p<0.001$, whole-brian corrected (WBC)). During the neutral condition, TR showed hyperactivity in the left hippocampus ($p<0.01$, WBC). During the 30 day follow-up, TR reported higher daily stress ($p<0.05$), difficulty controlling emotion ($p<0.05$) and frequent physical pain symptoms ($p<0.01$), compared to HC. Physical symptoms were predicted by hyperactive limbic response. Increased amygdala response to stress ($r=.49$; $p<0.05$) and hyperactive hippocampal response to neutral ($r=.52$; $p<0.01$) were associated with greater daily experience of physical symptoms during the follow-up. The current study demonstrated a strong link between trauma, hyperactive limbic response, and daily experience of stress and pain. Trauma may sensitize the stress-pain circuit localized in the limbic system and heighten stress and pain sensitivity. Sensitized limbic networks are likely to compromise its modulatory control over the stress, autonomic and immune pathways, thereby increasing adverse health symptoms. Individuals with a history of trauma may be at a greater risk of other emotional and physical disorders, resulting from altered limbic functions.

Disclosures: D. Seo: None. **R. Douglas:** None. **C. Larkin:** None. **S. Hwang:** None. **C. Lacadie:** None. **R. Sinha:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.02

Topic: F.04. Stress and the Brain

Support: US Highbush Blueberry Council- Effect of whole blueberry powder consumption on depression: A Randomized double-blind placebo controlled study
American Heart Association Grant-in-Aid: Role of HMGB1 in hypertensive response
NIH RO1 HL115208-01A1

Title: Transcriptomic changes in the dorsal hippocampus underlying avoidance behavior in a predator urine exposure model of PTSD

Authors: *D. P. KELLEY[1], D. SINGH[1], L. ALBRECHET-SOUZA[2], N. W. GILPIN[2], J. FRANCIS[1];
[1]Comparative Biomed. Sci., Louisiana State Univ., Baton Rouge, LA; [2]Physiol., Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA

Abstract: Post Traumatic Stress Disorder (PTSD) is associated with reduced hippocampal volume and alterations to contextual processing in both human patients and animal models, a process mediated by the dorsal hippocampus. Utilizing a bobcat urine exposure model of PTSD in rats, we investigated transcriptional differences in the dorsal hippocampus between control and exposed animals that either avoid (avoiders) or do not avoid (non-avoiders) a predator urine exposed context 16 days after the trauma, even after exploring the context in safety. Using KEGG pathway analysis, we evaluated differentially expressed genes (DEG) between control and all predator urine exposed animals (PUE), between control and avoider animals, between control and non-avoider animals, and between avoider and non-avoider animals. Numerous pathways were upregulated and several were downregulated between avoiders and non-avoider animals, in many cases due to divergent responses to trauma. Notable pathways include synapse associated pathways that were downregulated in avoiders compared to non-avoiders and translational and mitochondrial energy production related pathways that were upregulated in non-avoiders compared to avoiders. We also performed a post-hoc regression analysis across 4 notable pathways (synapse downregulated, synapse upregulated, translation, and mitochondria inner membrane) using differentially expressed genes to predict avoidance behavior. The post-hoc analysis yielded several potential pharmacological targets that could be investigated as novel therapeutics for PTSD. We are also in the process of investigating the same groups at just two days after trauma as well as females at both time points in order to determine the time course of these changes in addition to potential gender differences.

Disclosures: D.P. Kelley: None. **D. Singh:** None. **L. Albrechet-Souza:** None. **N.W. Gilpin:** None. **J. Francis:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.03

Topic: F.04. Stress and the Brain

Title: Microbiota transfer therapy reverses the effects of early life stress on hippocampal neurogenesis, HPA axis and metabolic risk in rats

Authors: *N. LAJUD[1], R. RUIZ GONZÁLEZ[1], D. L. DIAZ[2], E. PINEDA[2], A. ROQUE[2]; [1]Div. de Neurociencias, Ctr. de Investigacion Biomedica de Michoacan, [2]Inst. Mexicano del Seguro Social, Morelia, Mexico

Abstract: Early life stress (ELS) causes a decrease in hippocampal neurogenesis that is related to a dysregulation of the hypothalamus- pituitary- adrenal (HPA) axis and increased vulnerability to depression and metabolic risk. Recently it has been shown that ELS affects gut microbiota and treatment with probiotics during early life could prevent some of ELS effects; however weather reversing gut dysbiosis in adult individuals that already present ELS-induced alterations remains unclear. Hence the aim of the study was to test the hypothesis that microbiota transfer therapy (MTT) could reverse the effects of ELS. Adult control or maternally separated (MS180, 3hr / day from postnatal day one to 14) rats were subjected to microbiota depletion with oral antibiotics for one month (secondary abiotic) and then received MTT from donor animals by co- habitation. We evaluated depressive- like behavior in the forced swimming test, glucose homeostasis, plasma corticosterone concentrations, body weight, hippocampal neurogenesis and the relative abundance of bacterial species representative of the gut microbiota after microbiota depletion and again after MTT. Our results show that MS180 causes a passive coping strategy in the forced swimming test, increases metabolic risk, decreases hippocampal neurogenesis and causes intestinal dysbiosis. The depletion of the microbiota has similar effects to MS180 on behavior, corticosterone and hippocampal neurogenesis, however, it does not affect the glucose homeostasis or body weight. One month after the start of co- co habitation, MTT from control donors to MS180 rats reverses the effects of ELS on behavior, glucose homeostasis, and corticosterone; however it only attenuated the effects of hippocampal of ELS on neurogenesis. Moreover, these phenotypic differences were related to changes in relative abundance of *Lactobacillus* spp. and *B. fragilis*. In conclusion, our results indicate that reversing gut dysbiosis by MTT could be an effective therapeutic strategy aimed to reverse the effects of ELS in adult individuals.

Disclosures: N. Lajud: None. **R. Ruiz González:** None. **D.L. Diaz:** None. **A. Roque:** None. **E. Pineda:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.04

Topic: F.04. Stress and the Brain

Support: National Natural Science Foundation of China 81425010
National Natural Science Foundation of China 31630031
National Natural Science Foundation of China 91632303
External Cooperation Program of the Chinese Academy of Sciences GJHz1508
Guangdong Key Lab of Brain Connectome and Behaviour 2017B030301017

Title: A GABAergic neurocircuit that regulates glucose levels as part of the stress response

Authors: *X. JIA[1], S. TAO[2], F. XU[2], Z. LU[1], L. WANG[1];
[1]Shenzhen Inst. of Advanced Technology, Chines, Shenzhen, China; [2]Wuhan Inst. of Physics and Mathematics, Ctr. for Excellence in Brain Sci., Wuhan, China

Abstract: Stress is a risk factor for morbidity and mortality in metabolic disorders. However, the role of gamma amino butyric acid (GABA) ergic neurocircuits, recruited for the stress response, in regulating acute glucose levels remains unexplored. Here, we demonstrate that a GABAergic projection from the anterior bed nucleus of the stria terminalis (aBNST) to the arcuate nucleus (ARC)-a stress-producing circuit-induces acute hyperglycaemia via the sympathetic system. Optogenetic activation of the aBNST^{Gad2}-ARC pathway evokes anxiety-like behavioural states in synchronization with acute hyperglycaemia. Inhibition of the aBNST^{Gad2}-ARC pathway elicits an anxiolytic effect and blocks the hyperglycaemia induced by restraint stress. Conversely, adrenalectomy did not block the hyperglycaemia induced by activation of the aBNST^{Gad2}-ARC pathway. Pharmacogenetic inhibition of the ARC GABAergic neurons specifically projecting to the Raphe obscurus nucleus (ROb), followed by optical stimulation of the aBNST^{Gad2}-ARC pathway, dramatically decreased and depressed glucose levels. Our results reveal that a GABAergic circuit (i.e., aBNST-ARC-ROb) is recruited for the stress response and mobilizes glucose through the sympathetic system. This study highlights promising therapeutic targets for treating energy disturbances underlying stress.

Disclosures: **X. Jia:** None. **S. Tao:** None. **F. Xu:** None. **Z. Lu:** None. **L. Wang:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.05

Topic: F.04. Stress and the Brain

Support: NARSAD Young Investigator Award
Uniuversity of Cincinnati Neurobiology Research Center

Title: Lamina-specific microglia phenotypes are associated with synaptic deficits in the prefrontal cortex following chronic stress

Authors: J. L. BOLLINGER, S. C. WOODBURN, ***E. S. WOHLEB**;
Pharmacol. and Systems Physiol., Univ. of Cincinnati Col. of Med., Cincinnati, OH

Abstract: Chronic stress causes neuronal atrophy and synapse loss in the medial prefrontal cortex (PFC), which contributes to impaired PFC function and behavioral consequences. Preclinial studies indicate that stress-induced synapse loss is apparent on apical - but not basal - dendrites of pyramidal neurons in the medial PFC. Notably, apical dendrites extend to lamina (L)I of the cortex, while basal dendrites are confined to lamina (L)V. This is important because our recent work shows that microglia contribute to stress-induced neuronal remodeling in LI - but not LV - of the medial PFC. In this context, we hypothesized that lamina-specific microglia functions contribute to divergent stress effects on dendritic remodeling in the medial PFC. To test this hypothesis, mice were exposed to 14 days of chronic unpredictable stress (CUS) or handled intermittently as controls. Consistent with prior studies, confocal microscopy in Thy1-GFP(M) mice showed that CUS reduced spine density on apical (LI) - but not basal (LV) - dendrites of pyramidal neurons in the medial PFC. These synaptic deficits were associated with increased microglia-mediated neuronal remodeling in LI - but not LV - of the medial PFC. Further analyses using fluorescence-activated cell sorting (FACS) revealed that microglia in superficial PFC laminae (LI-III) have increased basal expression of *Csf1r*, *Cd11b*, and *Tnfa* as compared to microglia in deep laminae (LIV-V). Furthermore, CUS increased *Csf1r*, *Cd11b*, and *P2ry12*, and reduced *Tnfa* in microglia from superficial laminae (LI-III). Ongoing studies are using pharmacological interventions to test the role of P2RY12 signaling in neuron-microglia interactions and behavioral consequences following chronic stress. Altogether, these results provide initial evidence that lamina-specific microglia phenotypes may direct dendritic remodeling in the PFC and subsequent behavioral consequences

Disclosures: J.L. Bollinger: None. **S.C. Woodburn:** None. **E.S. Wohleb:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.06

Topic: F.04. Stress and the Brain

Support: University of Cincinnati Neurobiology Research Center
NARSAD Young Investigator Grant

Title: Chronic stress promotes sex-specific alterations in microglia and astrocyte function that are associated with synaptic deficits and behavioral consequences

Authors: *S. C. WOODBURN, M. HORCHAR, J. L. BOLLINGER, E. S. WOHLEB; Pharmacol. and Systems Physiol., Univ. of Cincinnati Col. of Med., Cincinnati, OH

Abstract: Clinical and preclinical research indicates that chronic stress causes neuronal atrophy and synapse loss in the prefrontal cortex (PFC), which leads to impaired PFC function. This is important because PFC dysfunction contributes to development of behavioral despair and working memory deficits. Interestingly, stress-induced synaptic deficits are linked to functional alterations in microglia and astrocytes in the PFC. For instance, chronic stress is shown to drive astrocyte dystrophy and microglia-mediated neuronal remodeling, which in turn contributes to stress-induced synaptic deficits in the PFC. Despite these findings, the temporal dynamics of stress-induced glial dysfunction and synaptic deficits in the PFC remain unclear. In these studies, male and female mice were exposed to varied durations of chronic unpredictable stress (CUS) to assess the molecular and cellular adaptations of neurons, microglia, and astrocytes. As expected, 14 days of CUS caused increased immobility in the forced swim test (FST) and reduced discrimination in temporal object recognition (TOR). These behavioral and cognitive impairments were associated with decreased dendritic spine density in the PFC of male, but not female mice. Further analyses revealed that 14 days of CUS decreased mRNA levels of *Gfap*, *Eaat1*, and *Tgfb2* in sorted PFC astrocytes from male, but not female, mice. In addition, 14 days of CUS increased mRNA levels of *Csf1r*, *Cd11b*, and *Cx3cr1* in sorted PFC microglia from male mice. After extended CUS exposure (28 days) both male and female mice displayed behavioral and cognitive impairments, and reduced synaptic density in the PFC. Notably, markers of astrocyte dystrophy persisted in male, but not female, mice. Furthermore, sorted PFC microglia from male mice showed normalization of genes associated with neuronal remodeling. These findings demonstrate that CUS causes sex-specific glial dysfunction that is associated with synaptic deficits and behavioral consequences. Further our results implicate microglia in early stages of stress-induced neuronal remodeling in male, but not female, mice. Future studies will elucidate the dynamic, cell type-specific role of neurons, astrocytes, and microglia in stress-induced synaptic deficits and associated behavioral consequences.

Disclosures: S.C. Woodburn: None. **M. Horchar:** None. **J.L. Bollinger:** None. **E.S. Wohleb:** None.

Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.07

Topic: F.04. Stress and the Brain

Support: R01 HD079520
R01 HD086085
Science Foundation Arizona

Title: Sensitive period for epigenetic consequences of early attachment on immune genes

Authors: *C. R. LEWIS[1], H. A. SOWARDS[2], L. D. DOANE[3], K. LEMERY-CHALFANT[2], M. J. HUENTELMAN[4];
[1]Translational Genomics Res. Inst., Phoenix, AZ; [3]Psychology, [2]Arizona State Univ., Tempe, AZ; [4]Neurogenomics, The Translational Genomics Res. Inst., Phoenix, AZ

Abstract: Individuals who experienced early attachment insecurity are at higher risk for health issues later in life. Insecure attachment in infants, school-age children, and adolescents is associated with maladaptive cortisol output from the hypothalamic-pituitary-adrenal (HPA) axis, which is associated with a variety of disorders. Immune dysregulation is one potential pathway explaining this link as the HPA and immune systems interact bi-directionally. The immune system consists of a network of cells, tissues and organs that protect the body from infection and disease. Social relationships (e.g. social isolation, loneliness, social support, conflict) influence measures of the immune system, including markers of inflammation and cellular immunity. To date, only a handful of studies have examined how attachment might influence immune processes, but there is growing interest in this important health question. Because recent evidence suggests that early social experiences prime HPA function via altering the epigenetic profile of regulatory genes, we hypothesized early life attachment may influence DNA methylation of immune-system genes in middle childhood. In the current study, we investigated the relationship between an indicator of attachment at 1 and 2.5 years and DNA methylation of 21 immune genes at 8.5 years old with monozygotic (MZ) twins (e.g. *IL6*, *CRP*, *TNF*, *NFKB1*). The MZ twin difference design controls for the influence of genotype on epigenetic status, allowing us to isolate variance in methylation due to environmental factors. Our sample included 96 MZ twins (51% male; 50% Non-Hispanic White, 14.6% Hispanic/Latinx, 8.3% African American, 4.2% Asian American) recruited from state birth records. Attachment was measured with reliable and valid primary-caregiver self-report (Emotional Availability Scale). Methylation was quantified from buccal cells using the Infinium Methylation EPIC BeadChip. We extracted the first two principal components from methylation of CpG sites within candidate genes. We computed MZ difference scores for attachment and methylation for linear regression analysis controlling for sex, array, and cell heterogeneity. We found attachment at 1 year predicted methylation of 18/21 genes (10 survived FDR p-value correction) six years later, whereas attachment at 2.5 years only predicted methylation of 1/21 gene. This age difference suggests that infancy may be a critical period when DNA methylation of immune genes is most sensitive to social cues from the environment. Our results suggest that DNA methylation of immune genes

may be a potential molecular mechanism by which early attachment affects long-term health outcomes.

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Nanosymposium

451. Stress and Trauma: Adaptive Mechanisms

Location: Room S404

Time: Tuesday, October 22, 2019, 8:00 AM - 10:00 AM

Presentation Number: 451.08

Topic: F.04. Stress and the Brain

Support: Quinnipiac University
NARSAD

Title: Maternal separation and *in utero* stress induces inflammation and microglia activation in the hippocampus of male and female rats

Authors: *A. J. B. BETZ[1], K. S. JONES[2], K. CONNOLLY[3], T. ZARIN[1], S. JACQUELINE[3], G. BURMAN[3], J. MIRRA[3], L. TELISKA[1], M. MIRRIONE[1];
[2]Psychology, [1]Quinnipiac Univ., Hamden, CT; [3]Quinnipiac Univ., New Haven, CT

Abstract: Early life experiences and chronic stress have pronounced effects on brain function and behavior. Maternal separation in rodents is a widely accepted animal model used to induce early-life stress. This model has reliably demonstrated an increased risk of depressive-like behavior later in life. Clinically, adversity in early life increases the risk for the development of psychiatric disorders, such as Major Depressive Disorder (MDD), in adulthood. Mood disorders produce changes in neurochemistry and brain structure in regions associated with learning and memory. Further, patients with MDD exhibit learning and memory deficits. In addition to changes in hippocampal volume, patients with MDD have been found to have elevated levels of peripheral and central inflammatory factors including IL-6 and TNFa. Microglial activity has been associated with atrophy and inflammatory signaling in brain regions affected by MDD. Given that patients with MDD display alterations in hippocampal circuits, we hypothesized that early life adversity would be characterized by increased protein expression of inflammatory markers, morphological changes in microglia and dynamic changes in cellular matrix activity in the hippocampus. Further, we proposed *in utero* exposure to stress would exacerbate these findings. In the present study, Sprague Dawley male and female pups were separated from PND 2 to PND 14 for three hours a day with and without lactational minocycline exposure or with and without *in utero* stress. A control condition of non- separated pups was maintained. First, we examined behavioral tasks during adolescence and found separated offspring spent more time in closed arms of an elevated plus maze. This was reversed with minocycline exposure and

exacerbated with *in utero* stress exposure. Second, we found preferential activation of RelA protein expression and other inflammatory markers in distinct compartments of the hippocampus following maternal separation. Finally, to understand the functional connectivity of our findings, we used immunofluorecence to examine the morphology of Iba1 positive cells and found increased ameboid shaped cells in the ventral hippocampus of male offspring. Overall, our results may provide insight to the molecular mechanisms responsible for inflammation and cellular reorganization in cortico-limbic circuits related to MDD from early life adversity and stress exposure.

Disclosures: **A.J.B. Betz:** None. **K.S. Jones:** None. **K. Connolly:** None. **T. Zarin:** None. **S. Jacqueline:** None. **G. Burman:** None. **J. Mirra:** None. **L. Teliska:** None. **M. Mirrione:** None.

Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 452.01

Topic: F.10. Food Intake and Energy Balance

Support: Department of Veterans Affairs (VA) Rehabilitation Research and Development (RRD) Career Development Award Level 2 (CDA2) Grant IK2 RX001817
VA Foundation, Louis Stokes VA Medical Center (Cleveland, OH) Pilot Grant
Clinical and Translational Science Collaborative, Case Western Reserve University (Cleveland, OH) Pilot Grant
Brain Rehabilitation Research Center (BRRC), Malcom Randall VA Medical Center (Gainesville, FL)

Title: Vagal tone changes associated with stomach distention and chronic diet

Authors: *M. A. SCHIEFER;
Malcom Randall VA Med. Ctr., Gainesville, FL

Abstract: Vagal nerve stimulation (VNS) provides a possible method to treat obesity. VNS has reduced excess body weight (EBW) in pre-clinical and clinical studies. Effective VNS stimulus parameters vary widely and it remains unclear how VNS should be used to reduce EBW, with some promoting activation while others promote inhibition. Outcomes may be improved by developing a bio-inspired stimulus pattern based on the neural response to stomach distension. While vagal activity is effected by intragastric pressure in healthy animals, these animals may not represent an obese population that has subsisted on a high fat diet for an extended duration. In this study, obesity prone Sprague Dawley rats were kept on an extended high fat diet between 100 and 300 days. At the time of the experiment, the rat was placed on a surgical plane of anesthesia with inhaled isoflurane. The abdomen was opened and a small incision made in the

wall of the stomach. A balloon catheter was inserted through the wall of the stomach, which was then sutured closed around the catheter. The other end of the catheter was attached to a programmable syringe pump. The cervical vagal nerve was exposed and a recording microelectrode array (MEA) was positioned next to the nerve. Up to 16 microelectrodes were inserted into the nerve. While recording from the MEA, the syringe pump was used to distend the stomach in fixed volumes designed to mimic eating. The stomach was distended to 5.0 mL in up to 50 0.1 mL distensions. Baseline activity was recorded for up to 300 seconds prior to initial distension. The power in the recorded signal was calculated to quantify vagal tone. Because each stomach was a different size, stomach distension was subsequently categorized as baseline (0 mL), minor (0.1-1.5 mL), moderate (1.5-3.0 mL) or major (>3.0 mL). Results were compared against rats kept on a control diet. Stomach volume and diet type effected the power within the recorded signal. There was a significant increase in power between baseline, minor, moderate, and major distension. Rats kept on a low fat (control) diet were found to have a significantly greater power than animals kept on a high fat diet, which is consistent with other studies that found that a high fat diet is associated with a reduced spike rate in the vagal nerve. While the precise neural contribution to satiety remains unknown, if a minimal vagal tone is required to produce a sense of stretch-mediated satiety, then the results suggest that an animal on a high fat diet would need to consume a greater volume of food to achieve this tone. This, too, is consistent with studies that investigated food consumption behavior.

Disclosures: M.A. Schiefer: None.

Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 452.02

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant R01DK056132
NIH Grant T32GM118292

Title: Fibroblast growth factor 19 in the dorsal vagal complex alters excitability of dorsal vagal motor neurons and lowers blood glucose concentration

Authors: *J. B. WEAN[1], B. N. SMITH[2];
[1]Physiol., [2]Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: According to the CDC, there are more than 30 million Americans living with diabetes. Although most diabetes research focuses on defects in insulin and glucose metabolism, 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 administered to the brain, 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 candidate region mediating the observed antidiabetic effects. Here, FGF19 (137µM) was shown to significantly decrease blood glucose concentration for up to 12 hours when administered to the DVC via fourth ventricular microinjection in type 1 diabetic mice (STZ). To understand the effects of FGF19 on DMV neuron excitability, patch-clamp electrophysiology was used in acute brainstem slices. FGF19 (230pM) altered action potential frequency, post-synaptic current frequency, and voltage-gated potassium current amplitude, all trending towards reduced excitability. These cellular effects are consistent with the hypothesis that FGF19 modifies central vagal circuitry controlling parasympathetic output to the viscera and could contribute to the peptide's effects on metabolism. Further studies are underway exploring the effects of FGF19 on DMV neuron excitability and peripheral glucose metabolism in diabetic mice.

Disclosures: J.B. Wean: None. **B.N. Smith:** None.

Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 452.03

Topic: F.10. Food Intake and Energy Balance

Support: Robertson Therapeutic Developmend Fund

Title: The dorsal raphe nucleus: A novel therapeutic entity for energy balance disorders

Authors: *M. SCHNEEBERGER PANE[1], L. PAROLARI[1], T. DAS BANERJEE[2], V. M. BHAVE[2], P. WANG[1], E. ENGEL[2], K. PELLEGRINO[1], C. J. CHOI[1], B. PATEL[2], T. TOPILKO[3], X. YU[1], P. COHEN[1], N. RENIER[3], A. R. NECTOW[2], J. M. FRIEDMAN[1]; [1]The Rockefeller Univ., New York, NY; [2]Princeton Univ., Princeton, NJ; [3]ICM, Paris, France

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. In order to identify all regions in the brain activated by heat/cold and ad libitum fed/fasting we used an unbiased whole-brain activity mapping system (iDISCO+). Interestingly, a previously unidentified region activated by heat was amongst the significantly enriched regions, the dorsal raphe nucleus (DRN). We demonstrated that this region

is important in regulating feeding and all parameters of energy expenditure, including thermogenesis.We show that GABAergic neurons in the dorsolateral portion of the DRN (hereafter, DRN^{Vgat}neurons) are activated by ambient heat and fasting and polysynaptically innervate interscapular brown adipose tissue (iBAT). Optogenetic and chemogenetic modulation of these neurons enables bidirectional regulation of energy intake and energy expenditure through changes in feeding, locomotion activity and 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 feeding and iBAT thermogenesis through downstream circuits in the hypothalamus and extended amygdala. On a separate set of experiments, we also demonstrated that glutamatergic neurons in the DRN, defined by the marker Vglut3, are activated by satiety signals and when stimulated suppress food intakeTogether, our work established that the DRN as a key nucleus in the control of energy balance.Here, we first identify through a combination of molecular profiling technology VTRAP and electrophysiological recordings that the DRN has specific druggable transmembrane receptors (to hormones or GPCRs) interesting for obesity therapy. Next, by means of pharmacology targeted to these receptors we identify drugs able to modulate specific food intake and body weight chronically.**References:***Nectow AR, **Schneeberger M (co-first)**, Zhang H, Field BC, Renier N, Azevedo E, Patel B, Liang Y, Mitra S, Tessier-Lavigne M, Han MH, Friedman JM.Identification of a brainstem circuit controlling feeding.**Cell**, Jul 27;170(3):429-442.e11. **Schneeberger M.** et al. Regulation of Energy Expenditure by Brainstem GABA Neurons. **In revision.***

Disclosures: **M. Schneeberger Pane:** None. **L. Parolari:** None. **T. Das Banerjee:** None. **V.M. Bhave:** None. **P. Wang:** None. **E. Engel:** None. **K. Pellegrino:** None. **C.J. Choi:** None. **B. Patel:** None. **T. Topilko:** None. **X. Yu:** None. **P. Cohen:** None. **N. Renier:** None. **A.R. Nectow:** None. **J.M. Friedman:** None.

Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 452.04

Topic: F.10. Food Intake and Energy Balance

Support: F32 HD095620

Title: Melanocortin 3 receptor engages AgRP circuitry to regulate feeding and anxiety

Authors: *P. SWEENEY[1], M. BEDENBAUGH[2], R. B. SIMERLY[3], P. GRIECO[4], R. D. CONE[1];
[1]Univ. of Michigan, Ann Arbor, MI; [3]Mol. Physiol. & Biophysics, [2]Vanderbilt Univ., Nashville, TN; [4]Univ. of Naples Federico II, Naples, Italy

Abstract: Disorders of negative energy balance, such as anorexia nervosa and disease cachexia, are characterized by decreased food intake, dangerously low BMI, and an increased risk of anxiety and depression. Despite the severe consequences of these disorders, few pharmacological strategies exist to stimulate feeding and reduce anxiety in these at-risk patient populations. A large body of research has established the critical role of hypothalamic AgRP neural circuits in stimulating feeding and behavioral studies have shown that activation of AgRP circuits also suppresses competing motivational states. The utility of stimulating these pathways in conditions of negative energy balance, such as anorexia nervosa or disease cachexia, warrants study. Here, we report that newly characterized MC3R agonists potently stimulate feeding, increase body weight, and reduce anxiety in an AgRP neuron dependent manner. Consistently, we identify that the MC3R is highly expressed in arcuate AgRP neurons, with significantly higher expression in these cells than anorexigenic POMC neurons. Chemogenetic activation of arcuate MC3R neurons both stimulates feeding and body weight and reduces anxiety-related behavior. Pharmacological stimulation of the MC3R phenocopies the increased food intake and reduced anxiety observed following chemogenetic activation of arcuate MC3R neurons. Conversely, chemogenetic inhibition of arcuate MC3R neurons reduces feeding and increases anxiety-related behavior. Finally, we demonstrate that mice lacking the MC3R display multiple behavioral phenotypes resembling anorexia nervosa, such as enhanced anxiety behavior and increased susceptibility to multiple forms of stress-induced anorexia. Taken together, these results suggest that stimulation of the MC3R is a promising therapeutic approach for combating disorders at the intersection of energy metabolism and emotion, such as anorexia nervosa.

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Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

Time: Tuesday, October 22, 2019, 8:00 AM - 9:45 AM

Presentation Number: 452.05

Topic: F.10. Food Intake and Energy Balance

Title: Interrogating the role of AgRP neurons in the pathogenesis of activity-based anorexia

Authors: *A. K. SUTTON, M. J. KRASHES;
NIH, Bethesda, MD

Abstract: An individual’s level of motivation to seek out and subsequently eat food is flexible and dependent on a variety of internal and external factors. These can include energetic demands, threat perception, reproductive state, and social context. However, in situations with limited food supply, animals must position themselves for survival by limiting energy expenditure and promoting food intake. In the case that these adaptations are not achieved, maladaptive energy

balance occurs and subsequent disease states ensue, such as anorexia nervosa. Anorexia nervosa is a deadly psychiatric illness occurring in both humans and rodents that is often characterized by over-exercise without the appropriate increased food intake, resulting in substantial weight-loss and subsequent mortality. The central mechanisms resulting in this maladaptive behavioral process, despite being the most lethal psychiatric illness in the United States, are poorly understood. Accordingly, determining individual susceptibility or resistance to anorexia nervosa is severely lacking. Here, we use an established model of activity-based anorexia (ABA) in mice to investigate the putative mechanisms leading to the onset and possible disabling of anorexia development. Studies to date have demonstrated that hunger-promoting peptides, including agouti-related peptide (AgRP) in the arcuate nucleus of the hypothalamus, are not appropriately increased in response to food restriction in the presence of a running wheel. However, it is unknown whether dysregulation of this population of neurons leads to the development of activity-based anorexia. To test the role of AgRP neurons in ABA pathogenesis, we leverage cutting-edge, genetically-powered tools to acutely manipulate, monitor and map AgRP neurons before, during and after mice are exposed to this ABA protocol. Preliminary data suggests that chemogenetic activation of AgRP neurons is sufficient to rescue activity-based anorexia. Additional experiments are ongoing to determine the activity patterns of AgRP neurons (using both freely-moving photometry and single-cell *in vivo* two-photon calcium imaging) in response to food presentation following ABA challenge. Overall, our results suggest a role for hunger-promoting AgRP circuits in the rescue of activity-based anorexia. Thus, these results have the potential to promote the development of future treatments and prevention strategies for diseases associated with dysregulated feeding behavior in the face of food restriction, including anorexia nervosa.

Disclosures: A.K. Sutton: None. **M.J. Krashes:** None.

Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

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Presentation Number: 452.06

Topic: F.10. Food Intake and Energy Balance

Support: NIH DK 106476

Title: Exposure to maternal high-fat diet during lactation impairs the organization and activity of GLP-1 innervation to the paraventricular nucleus of the hypothalamus

Authors: *D. SRISAI[1], J. E. BIDDINGER[1], M. M. SCOTT[2], R. B. SIMERLY[1];
[1]Vanderbilt Univ., Nashville, TN; [2]Dept. of Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Perinatal exposure to maternal high fat diet (MHFD) causes significant changes in both levels and timing of postnatal leptin secretion in the offspring with adverse consequences for regulation of energy homeostasis. Restricting MHFD to the lactational period (MHFD-L) corresponds to the early postnatal leptin surge and is known to impair both metabolic physiology and hypothalamic circuitry (Vogt et al, 2014). Visceral sensory information is relayed to the hypothalamus by the nucleus of the solitary tract (NTS), which contains a population of preproglucagon (PPG) neurons that innervate the paraventricular nucleus of the hypothalamus (PVH), a region that integrates varied metabolic signals regulating energy balance. Glucagon-like peptide-1 (GLP-1) is expressed in these inputs to the PVH and signals through its receptor (GLP-1R). GLP-1R expressing PVH neurons, have been shown previously to respond to caloric state and acute feeding behavior suggesting that they play an important role in mediating satiety (Li et al., 2018). However, it remains unknown if MHFD-L impacts neuronal targeting of PPG neurons to the PVH, or if GLP-1 neuronal signaling is altered in the offspring. To address this question, we used immunohistochemistry to visualize GLP-1 projections to the PVH in offspring derived from dams exposed to MHFD-L. Exposure to MHFD-L caused a reduction in GLP-1 fiber density in the PVH by postnatal day 16 and this difference was maintained into adulthood. In addition, there was a reduction in cFos activation in PVH neurons following vagal activation by either i.p. injection of cholecystokinin (CCK) or stomach stretch induced by oral gavage. Whether reorganization of GLP-1 inputs to PVH neurons impacted the ensemble properties of GLP-1R neurons was confirmed by using microendoscopy and an Inscopix nVista miniaturized fluorescence microscope to image calcium dynamics in awake behaving mice. GCamP6s was targeted to GLP-1R neurons in the PVH and images collected through a GRIN lens (0.6mmx7.3mm) following i.p. injection of CCK or gastric distention. The results suggest that exposure to MHFD-L causes sustained changes in the ensemble responses of GLP-1R neurons in the PVH to diverse visceral sensory activation. Together, these findings indicate that exposure to MHFD-L is sufficient to cause lasting changes in the organization of visceral sensory pathways to the hypothalamus that permanently alter the input/output activity of central circuits regulating metabolic phenotype.

Disclosures: D. Srisai: None. **J.E. Biddinger:** None. **M.M. Scott:** None. **R.B. Simerly:** None.

Nanosymposium

452. Homeostatic Circuits, Feeding, and Energy Balance

Location: Room S505

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Presentation Number: 452.07

Topic: F.10. Food Intake and Energy Balance

Title: Hypothalamic glucagon like peptide regulates food intake

Authors: *J. LIU[1], K. M. CONDE[2], Z. XU[3], J. PHANSALKAR[3], M. M. SCOTT[5], Z. PANG[4]; [1]Natl. Engin. Lab. for Brain-inspired Intelligence Technol. and Application, Univ. of Sci. and Technol. of China, Hefei, China; [2]Rutgers Univ., North Brunswick, NJ; [4]Child Hlth. Inst. of New Jersey, [3]Rutgers Univ., New Brunswick, NJ; [5]Dept. of Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Glucagon Like Peptide 1 (GLP-1)-expressing neurons in the hindbrain send robust projections to the hypothalamus, including paraventricular nucleus of the hypothalamus (PVN) and dorsal medial hypothalamus (DMH), which are involved in the regulation of food intake. Here, we describe that stimulation of GLP-1 afferent fibers in both PVN and DMH are sufficient to suppress food intake independent of glutamate release. In the PVN, GLP-1 receptor (GLP-1R) activation augments excitatory synaptic strength in PVN corticotropin-releasing hormone (CRH) neurons, with GLP-1R activation promoting a protein kinase A (PKA) dependent signaling cascade leading to phosphorylation of serine S845 on GluA1 AMPA receptors and their trafficking to the plasma membrane. In the DMH, however, GLP-1R activation suppresses delayed rectifier voltage-gated potassium (Kv) channel, which results in depolarization of DMH neurons. This study provides a comprehensive multi-level (circuit, synaptic, and molecular) explanation of how food intake behavior and body weight are regulated by endogenous central GLP-1.

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Nanosymposium

453. Effects of Cocaine Use

Location: Room S401

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Topic: G.08. Drugs of Abuse and Addiction

Support: the National Natural Science Foundation of China Youth Fund (31500893)
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CAS Key Laboratory of Mental Health, Institute of Psychology (KLMH2018ZG05)

Title: Drug seeking motivation in tree shrews after cocaine abstinence enhanced by dopamine D1 receptor mediated upregulation of Cav1.2 in the nucleus accumbens

Authors: *F. SHEN[1,2], Y. DUAN[1,2], Y. MENG[1,2], W. DU[1,2], J. ZHANG[1,2], J. LIANG[1,2], Y. LI[1,2], M. LI[3], N. SUI[1,2];
[1]Key Lab. of Mental Hlth., Inst. of Psychology, CAS, Beijing City, China; [2]Inst. of Psychology,UCAS, Beijing City, China; [3]Dept. of Psychology, Univ. of Nebraska-Lincoln, Lincoln, NE

Abstract: After a long-term abstinence from drug use, animals tend to exhibit an increase in motivation in drug-seeking behavior. This incubation-induced increase in drug-seeking is closely related to the altered expression of dopamine (DA) receptors. Because DA receptors also dynamically regulate L-type calcium channels (LTCCs), which could have a direct modulatory effect on neuronal excitability, we examined how manipulation of DA receptors (D1R or D2R) and LTCCs functions influences of cocaine-seeking in tree shrew model, a near-primate animal model sensitive to operational conditioned training. First, we found that adult male tree shrews exhibited a significantly higher breakpoint in cocaine self-administration after 45 withdrawal days. Next, we found that LTCCs inhibitor verapamil reduced the number of cocaine seeking behavior. Moreover, activation of $Ca_v1.2$, but not $Ca_v1.3$, facilitated the formation and expression of cocaine self-administration after long-term abstinence. Finally, we found that the up-regulation of D1R protein expression, but not D2R, increased cocaine self-administration and up-regulated $Ca_v1.2$. These findings suggest that D1R-mediated up-regulation of calcium $Ca_v1.2$ channels may mediate the incubation-induced increase in motivation in cocaine-seeking behavior, suggesting that the calcium $Ca_v1.2$ channels may be a viable molecular target for the treatment of cocaine addiction.

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Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: 1K99DA046522-01A1
NIH DA 003906
NIH DA12513

Title: Nucleus accumbens neuronal ensembles in cue-induced reward seeking

Authors: *A.-C. BOBADILLA[1], E. DERESCHEWITZ[1], M. D. SCOFIELD[2], J. A. HEINSBROEK[3], P. W. KALIVAS[1];

[1]Neurosci., [2]Anesthesia and Perioperative Med., Med. Univ. of South Carolina, Charleston, SC; [3]Anesthesiol., Univ. of Colorado Denver - Anschutz Med. Campus, Aurora, CO

Abstract: Unmanaged reward seeking is a shared central feature of eating and substance use disorders. Recent research shows that rewarding drug-related experiences induce synchronous activation of a discrete number of neurons in the nucleus accumbens (NAcc) that are causally linked to reward-related contexts. These results suggest a finely tuned specificity of ensembles. Here we characterized the neuronal ensemble that is built through drug experience and codes for drug seeking. We additionally address the question of whether or not addictive drugs usurp circuitry used by natural rewards or involve distinct circuitry mechanisms by evaluating the segregation between cocaine- and sucrose-related ensembles within the same animal. We use targeted recombination in active populations (TRAP) strategy, specifically $Fos^{CreERT2/+}$/Ai14 (cFos-TRAP) transgenic mice to tag cells as potentially encoding these behaviors. To define and compare different reward-specific ensembles within the same animal, we developed a dual cocaine and sucrose self-administration (SA) paradigm in mice, where each reward is associated to a different discrete cue. Using this paradigm, we were able to assess the neurons included in the cocaine or sucrose ensembles, and to quantify the overlap between the two populations within the same animal exposed to both types of reward. Moreover, we used RNAscope to determine the cell types included in the seeking ensembles. We tagged with tdTomato the small number of neurons in the NAcore activated during repeated cued-induced seeking to cocaine or sucrose. The tdTomato cells were specifically activated during seeking, and not during extinction behavior or after animals remained in the home cage. Moreover, we validated the dual cocaine and sucrose SA paradigm, and were able to compare the overlap of reward-specific seeking ensembles in animals previously exposed to both rewards.

Disclosures: **A. Bobadilla:** A. Employment/Salary (full or part-time):; MUSC. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIDA 1K99DA046522-01A1. **E. Dereschewitz:** A. Employment/Salary (full or part-time):; MUSC. **M.D. Scofield:** A. Employment/Salary (full or part-time):; MUSC. **J.A. Heinsbroek:** None. **P.W. Kalivas:** A. Employment/Salary (full or part-time):; MUSC. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH DA 003906 and DA12513.

Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

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T32007135
R01DA041528

Title: Longitudinal assessments of incubation of cue-induced drug craving in cocaine-addicted individuals

Authors: *M. A. PARVAZ, R. A. RABIN, P. MALAKER, A. KALAJ, A. WAGNER, N. ALIA-KLEIN, R. Z. GOLDSTEIN;
Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: ***Background:*** Cue-induced craving is a major contributor to relapse in treatment-seeking addicted individuals. Animal studies have shown that cue-induced drug-seeking increases (or incubates) during the initial phase of abstinence, presumably reflecting a period of heightened relapse vulnerability. However, these findings have not been robustly translated, as most human studies show a steady decline in craving with increasing abstinence duration. In a previous cross-sectional study, we employed EEG-derived late positive potential (LPP) as a biomarker for cue-induced craving, providing evidence for incubation of cue-induced craving in cocaine addiction. Here, we used a within-subjects longitudinal design spanning 5 follow-ups acquired every 3 months over 12 months of abstinence in individuals with cocaine use disorders (iCUD) in an effort to robustly translate animal findings to human addiction.
Methods: Thirteen mostly treatment-seeking iCUD completed three assessments: at baseline (7-40 days), 3 months (55-96 days) and 6-months (110-185 days) after abstinence. At each visit, participants completed the Cocaine Craving Questionnaire to report their unprovoked subjective craving. In addition, EEG data were recorded to assess cue-reactivity as participants passively viewed 30 cocaine and 30 neutral pictures. For each picture, participants rated the intensity of cocaine 'wanting' (i.e., subjective cue-induced drug craving). The LPP elicited by cocaine-related relative to neutral pictures was extracted.
Results: As expected, subjective unprovoked craving decreased linearly [$F(1,12)=19.42$, $p=.001$] with abstinence. Interestingly, subjective cue-induced cocaine wanting ratings showed an inverted u-shaped quadratic effect [$F(1,19)=19.46$, $p=.011$] such that it was higher at 3 months relative to both baseline and 6-months follow-up. A similar pattern, albeit at a trend level, was also observed for the LPP amplitudes [$F(1,12)=2.86$, $p=.12$]. Analyses with longer time points (9 and 12 months) and more subjects are underway and novel results will be included in the conference presentation.
Conclusion: To our knowledge the current study is the first to use both subjective and objective indices to show longitudinal evidence of incubation and subsequent decline in cue-induced craving in iCUD. These results underscore the need for incorporating measures of cue-induced craving in addition to baseline measures, which are commonly used in clinical settings. Ultimately, we aim to identify precise time-courses of personalized craving trajectories that could be optimally targeted for individualized treatment deployment for preventing relapse.

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Nanosymposium

453. Effects of Cocaine Use

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Presentation Number: 453.04

Topic: G.08. Drugs of Abuse and Addiction

Support: DA031900

Title: Incubation of cocaine craving coincides with changes in dopamine terminal neurotransmission

Authors: *I. P. ALONSO, B. M. O'CONNOR, K. G. BRYANT, R. A. ESPAÑA;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Finding effective and tolerable treatments for cocaine addiction has been extremely challenging particularly because of the high rates of relapse. Clinical and animal studies have shown a progressive intensification of cocaine seeking and craving during abstinence, increasing the likelihood of relapse. In rodents this intensification of cocaine craving can be modeled via short access (ShA), long access (LgA) or intermittent access (IntA) self-administration schedule followed by prolonged abstinence. While the ShA and LgA models allow for mostly unfettered cocaine access across 2-h or 6-h sessions, respectively, the IntA model restricts access to 5 min bouts every 25 min for 6 h mimicking typical human cocaine use patterns. Furthermore, while dopamine (DA) terminal adaptations have been observed in these different schedules following training, to our knowledge no one has examined changes in DA neurotransmission after prolonged abstinence. In these experiments, male and female Sprague-Dawley rats underwent cocaine self-administration training on the ShA, LgA or IntA schedules and were tested for their motivation to seek cocaine on days 1 and 28 of abstinence. Changes in DA release, uptake, and cocaine-induced DA uptake inhibition were then recorded using fast scan cyclic voltammetry on day 29 of abstinence following the seeking test. Under the LgA and IntA schedules, a significant intensification of cocaine seeking after abstinence was observed. Consisted with this, rats exposed to IntA and LgA cocaine self-administration followed by abstinence showed an increase cocaine potency at the DA transporter. These results suggest that incubation of cocaine craving coincides with changes in dopaminergic transmission following the IntA and LgA behavioral paradigms. Understanding the relationship between changes in DA neurotransmission and intensification of cocaine seeking observed after abstinence may provide critical information for the development of therapeutic targets to prevent cocaine relapse.

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Title: Integrins and focal adhesion kinase as a signaling pathway for MMP-9 induction of transient synaptic plasticity in cocaine relapse

Authors: *C. GARCIA-KELLER[1], D. NEUHOFER[4], M. D. SCOFIELD[2], A.-C. BOBADILLA[3], C. MONFORTON[1], S. VARANASI[1], M. REEVES[1], P. W. KALIVAS[5]; [2]Neurosci., [3]Dept. of Neurosci., [1]Med. Univ. of South Carolina, Charleston, SC; [4]Neurosci., MUSC, Charleston, SC; [5]Neurosci. Res., Med. Univ. S Carolina, Charleston, SC

Abstract: Cocaine use elicits neuroplasticity within the nucleus accumbens core (NAcore) that leads to increased vulnerability to relapse, even after protracted abstinence. Matrix metalloproteinases (MMPs) are inducible endopeptidases that degrade extracellular matrix (ECM) proteins (such as fibronectin, laminin and thrombospondin) as well as non-ECM signaling molecules, and reveal an RGD domain that binds and signals through integrins. Integrins are heterodimeric receptors composed of αβ subunits, and their primary signaling kinases are the focal adhesion kinase (FAK) and integrin linked kinase (ILK). Previous results show that β3 integrin is upregulated after cocaine self-administration and MMP-9 activity is increased during cued-reinstatement of cocaine and promotes transient synaptic plasticity (t-SP: increases in spine head diameter (d_h) and AMPA/NMDA (A/N)). Here we endeavor to understand if β3 integrin signaling through FAK and cofilin (actin depolymerization factor) is necessary to promote synaptic growth and increased AMPA/NMDA ratio during t-SP produced during drug-seeking.
To study the increases of d_h and A/N induced by MMP-9 activation we use an antisense morpholino to reduce the expression of β3 Integrin and an small molecule inhibitor to prevent FAK and ILK activation during cued-reinstatement. β3 Integrin down-regulation and FAK inhibitor, but not ILK, blocked cued-reinstatement, d_h and A/N compared with scramble morpholino or vehicle. Using immunohistochemistry on NAcore labeled spines with ChR2-YFP virus, we showed MMP and β3-dependent FAK and cofilin phosphorylation, with an increased expression of p-FAK and p-cofilin in dendritic spines of reinstated cocaine animals compared to

extinguished and yoked-saline. Then, we specifically labeled D1 or D2 neurons with ChR2-mCherry using a viral approach in Cre^+ rats. We found that p-FAK is increased during drug seeking in D1 and D2-MSNs, although phosphorylation of cofilin by p-FAK was observed only in D1-MSNs. These data propose that β3 Integrin, FAK and cofilin constitute a signaling pathway downstream of MMPs activation that is involved in promoting transient synaptic growth induced by cocaine-conditioned cues that reinstate drug seeking, but not sucrose seeking.

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Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: DA 040965
P30 GM103398
P30 NS061800

Title: Changes in parvalbumin interneurons within the medial prefrontal cortex after a cocaine memory reactivation in rats following removal of perineuronal nets

Authors: *A. E. GONZALEZ[1], E. T. JORGENSEN[3], J. H. HARKNESS[5], A. DEAN[6], S. A. AICHER[7], D. M. HEGARTY[8], T. E. BROWN[4], B. A. SORG[2];
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Abstract: Parvalbumin (PV)-positive cells are GABAergic fast-spiking interneurons in the medial prefrontal cortex (mPFC). PV cells modulate the activity of pyramidal neurons and their output to other brain areas associated with learning and memory. A majority of PV cells are wrapped in a specialized extracellular matrix structure called the perineuronal net. We have previously found that removal of PNNs with the enzyme *chondroitinase ABC* (Ch-ABC) in the mPFC prevents the consolidation and reconsolidation of cocaine-associated memories. More recently, we have discovered that cocaine exposure and cocaine-associated memories alone can alter the integrity of PNNs and PV intensity in the mPFC. Here we examined the time course of changes in PV intensity following the reactivation of a cocaine-associated memory after removal

of PNNs. Rats were initially trained for cocaine-induced conditioned place preference (CPP) with three injections of saline (1 mL/kg, intraperitoneal, ip) alternating with three injections of cocaine (12 mg/kg, ip). Rats then underwent extinction training for at least 8 days. After the last extinction training, rats were microinjected with Ch-ABC in the prelimbic (PL) mPFC. Re-exposure to the CPP context occurred 72 hours later with a cocaine priming injection (10 mg/kg ip), and rats were sacrificed either 2 hr, 6 hr, or 48 hr later. A separate cohort of rats was sacrificed prior to any re-exposure as a baseline control (t = 0). Brain slices were stained and quantified for PV. We are currently measuring the intensity of PV and PNNs and excitatory and inhibitory puncta apposing PV cells surrounded by PNNs. Rats given Ch-ABC reinstated CPP to the same extent as vehicle controls following the cocaine priming injection.
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Topic: G.08. Drugs of Abuse and Addiction

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NIH Grant R37DA007359

Title: Epigenetic priming underlies transcriptional disruption linked to cocaine relapse

Authors: *P. MEWS[1], H. KRONMAN[1], A. RAMAKRISHNAN[1], S. SIDOLI[2], A. A. REYES[1], B. GARCIA[2], L. SHEN[1], E. J. NESTLER[1];
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Abstract: Drug addiction is a major public health crisis that exacts tremendous psychological and financial costs on patients, their families, and society at large. Drugs of abuse, despite their very different chemical structures and initial protein targets, ultimately converge by producing persistent plasticity and long-lasting changes in gene regulation in a central brain region of reward, the nucleus accumbens (NAc). Permanent changes in chromatin structure are hypothesized to underlie the transcriptional dysregulation that characterizes drug addiction; however, there is to date no direct link between drug-induced epigenetic alterations and the aberrant gene regulation that contributes to relapse. A fundamental challenge is to determine which neuronal subtypes are responsible: the NAc is composed of two opposing types of medium spiny neurons (MSNs), the D1 and D2 dopamine receptor-expressing subtypes, which

exhibit dramatic differences in activity and effects on drug reward. Here, we investigated the cocaine-induced changes in chromatin genome-wide by ATAC-seq in the distinct D1 and D2 MSN subtypes, and distinguished immediate versus persistent alterations in combination with unbiased histone modification profiling by mass spectrometry and ChIP-sequencing. We found that chronic cocaine persistently alters striatal chromatin structure, especially in D1 MSNs, involving eviction of the histone variant H2A.Z, a recently identified memory suppressor, at key neuronal genes. Curiously, genome accessibility in D1 MSNs is prominently increased at these 'scarred' genes even after prolonged periods of withdrawal, linked to long-lasting dysregulation of gene expression upon relapse. Together, our studies investigate an emerging view of epigenetic adaptation and gene dysfunction that may contribute to drug addiction, providing novel insight into epigenetic priming as an important mechanism whereby drugs of abuse alter brain function and behavior in lasting ways. Since epigenetic aberrations may be reversible, this mechanistic understanding of chromatin 'scarring' by drugs of abuse could pave the way to novel epigenetic interventions to treat drug addiction.

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Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Neuron subtype specific role of methylated DNA cytosine dioxygenase TET1 in cocaine addiction

Authors: *H. XU, G. KAPLAN, R. HEDINGER, J. FENG;
Florida State Univ., Tallahassee, FL

Abstract: The role of epigenetic mechanisms, such as DNA methylation, have been increasingly appreciated in drug addiction. Recently, additional forms of DNA epigenetic modifications have been identified through the oxidation of methylated DNA cytosine through their catalyzing enzymes, ten-eleven translocation proteins (TETs), which may lead to DNA demethylation. Though the three members of the TET family (TET1, TET2, TET3) are expressed in the adult brain, their role in drug addiction is still largely unknown. Previously, we found that TET1 in the nucleus accumbens (NAc) is implicated in cocaine action, suggesting a functional role of DNA modifications in cocaine addiction. In the present study, we investigated the impact of Tet1 deletion in either dopamine D1 receptor-expressing medium spiny neurons (D1-MSN) or

dopamine D2 receptor-expressing MSNs (D2-MSN) on cocaine-induced behavioral responding in mice. The rewarding effect of cocaine in mice with Tet1 knockout in D1- or D2-MSNs (D1-MSN or D2-MSN Tet1 KO) was evaluated using the conditioned place preference (CPP) paradigm, and cocaine addiction-like behavior was tested using an operant intra-venous self-administration (SFA) model. Furthermore, genome-wide DNA methylation profiling was analyzed in NAc D1-MSNs and D2-MSNs from both control and Tet1 KO mice. We discovered that D1-MSN Tet1 KO in male mice and D2-MSN Tet1 KO in female mice enhance the rewarding value of cocaine, potentiates the vulnerability to cocaine binge, and amplifies the incentive motivation for consuming cocaine. These findings suggest a neuron subtype-specific role of DNA epigenetic modifications in cocaine addiction.

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Nanosymposium

453. Effects of Cocaine Use

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Presentation Number: 453.09

Topic: G.08. Drugs of Abuse and Addiction

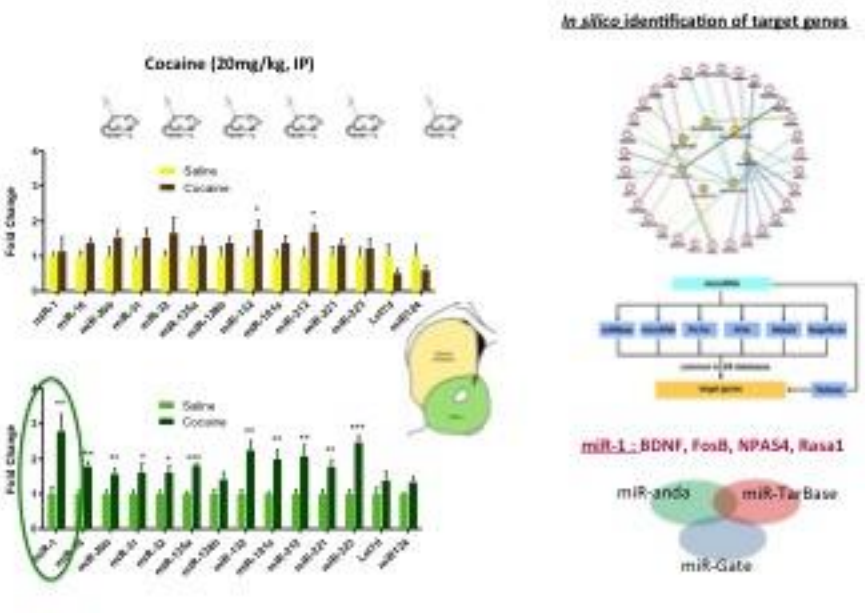
Support: Fondation pour la REcherche Médicale DEQ20150734352 to JC
Labex BioPsy : miRNAddict

Title: The non-coding RNA miR1 plays a cell-type specific role in molecular and behavioral adaptations to cocaine

Authors: B. FORGET[1], A. GODINO[2], E. MARTIN GARCIA[3], L. DOMINGO-RODRIGUEZ, Jr[3], P. POIRIER[1], V. KAPPES[1], P. VANHOUTTE[1], R. MALDONADO[3], ***J. CABOCHE**[1]; [1]1-Neurosciences Paris Seine, Sorbonne Universités, CNRS UMR8246/INSERM UMRS1130, PARIS CEDEX 05, France; [2]Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Laboratori de Neurofarmacologia-NeuroPhar Departament de Ciències Experimentals i de la Salut (DCEXS, Univ. Pompeu Fabra (UPF), Barcelona, Spain

Abstract: The persistent but nevertheless experience-dependent aspects of the addicted phenotype suggest a key role for epigenetic modifications in mediating the neuro-adaptive changes induced by drug exposure in the reward circuitry. These epigenetic mechanisms include micro-RNAs (miRNAs), a category of non-coding RNAs that are involved in physiological neuronal function and possibly altered in several psychiatric conditions, including addiction. In this study, we analyzed 12 plasticity-related miRNAs, selected based on their association with either addiction or other brain disorders. After chronic cocaine administration in mice, a subset of these miRNAs was up-regulated in the nucleus accumbens (NAc) but not in more dorsal parts of the striatum (DS), suggesting that these miRNAs could play a homeostatic role and oppose

drug-induced gene expression in the NAc. Among these, we identified miR1 *in silico* as a hub for regulating cocaine-plasticity associated genes, including BDNF, FosB and NPAS4, and further confirmed its regulatory role both *in vitro* and *in vivo*. Finally, we used an AAV-mediated strategy to over-express miR1 in Striatal Projection Neurons (SPNs) expressing either the D1 or D2 dopamine receptor in either the NAc or the DS before testing the behavioral responses to cocaine in mice. Inducing miR1 in D1R-SPN of the DS caused a decrease in the reinstatement of conditioned place preference induced by a non-contingent administration of cocaine after an extinction period. By contrast, miR1 in D1R-SPNs of the DS increased cue-induced reinstatement after contingent cocaine self-administration. Altogether, these data suggest a key role for miR1 in modulating relapse-like behaviors after cocaine withdrawal. They also highlight the complexity of gene regulation in D1R- versus D2R-SPNs, and the necessity to better dissect miRNA regulation in these striatal subpopulations, separately.



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Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: CIHR Fellowship 358810

Title: Dopamine receptor 3 signaling in the ventral pallidum drives persistent changes in neuronal activity and drug-seeking behavior following cocaine self-administration

Authors: *H. PRIBIAG, S. SHIN, E. WANG, P. HONMA, V. LILASCHAROEN, B. LIM; UCSD, La Jolla, CA

Abstract: Drug-induced plasticity of the reward system is thought to play a critical role in driving drug seeking during abstinence, yet how this process occurs across different mesolimbic targets is not well understood. Designing effective therapies that reduce persistent drug seeking requires an understanding of the neural circuits that are active during drug seeking, as well as knowledge of the drug-induced molecular factors that drive these changes in neural activity. We quantitatively measured gene expression changes induced by abstinence from cocaine exposure and identified a robust increase in the expression of dopamine receptor 3 (Drd3) in the ventral pallidum (VP). Experiments using fluorescent *in situ* hybridization determined that 40.9±3.6% of Drd3-expressing VP cells do not co-express Drd1 or Drd2, suggesting a different Drd3 signaling landscape as compared to the nucleus accumbens. Using viral-mediated anatomical tracing methods we found that VP Drd3 neurons are embedded within circuits implicated in the regulation of motivation and addiction. To understand the role of VP Drd3 signaling in drug seeking we used viral-mediated knock-down (KD) of Drd3 in the VP and measured seeking rates following prolonged abstinence from cocaine self-administration. Drd3 KD in the VP significantly reduced cocaine seeking, but did not alter the acquisition of self-administration behavior. To understand changes in neuronal activity underlying the development of drug-seeking behavior, we used *in vivo* $^{Ca2+}$ imaging to monitor the activity of VP Drd3 neurons during cocaine self-administration and during re-exposure to the cocaine self-administration context, in both control and VP Drd3 KD mice. Further experiments using chemogenetic manipulation suggested that VP Drd3 neuron activity makes a substantial contribution to driving cocaine seeking. Our results provide insight into the role of dopaminergic signaling in the VP and a cell-type specific understanding of how plasticity in the VP contributes to persistent drug seeking behavior.

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Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: ANR Grant ANR-15-CE16-0017
ANR Grant ANR-18-CE37-0003

Title: Dopamine and glutamate receptor heteromers: Modulation and roles in cocaine-evoked adaptations

Authors: *A. NJIVA ANDRY[1], E. SAINT JOUR[1], R. WALLE[2], Y. ZHU[3], J. BARIK[5], P. TRIFILIEFF[2], J. A. JAVITCH[4], J. CABOCHE[6], P. VANHOUTTE[1];
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Abstract: Drugs of abuse increase dopamine (DA) in the mesolimbic system, especially in the striatum, where it shapes the efficacy of glutamatergic synapses and contributes to long-lasting behavioral alterations. This integration of DA and Glutamate (Glu) inputs is achieved by striatal projection neurons (SPN), which form two mainly segregated populations: the “direct pathway” SPN (dSPN), expressing DA D1 receptors (D1R) that promotes reward, and the “indirect pathway” SPN (iSPN) that express DA D2 receptors (D2R) that inhibits reinforcement. We identified heteromers formed by the D1R with Glu NMDA (NMDAR) receptors as molecular bridges by which DA facilitate Glu-dependent synaptic transmission in dSPN. Conversely, others found that the D2R/NMDAR interaction mediates the inhibitory effect of DA on NMDAR-signaling in iSPN. However, the modulation and function of these heteromers in responses to cocaine are yet unknown. Using Proximity Ligation Assay, we found that cocaine-induced locomotor sensitization was associated with the formation D1R/NMDAR heteromers in the Nucleus Accumbens (NAcc) and the Dorsal Striatum, while D2R/GluN2B heteromerization was restricted to the NAcc. We also detected DAR/NMDAR complexes from human-post mortem caudate-putamen samples and describe their modulations in subjects with a history of dependence to psychostimulants. To identify the roles of DAR/NMDAR in the different phases of cocaine-mediated molecular, morphological and behavioral responses *in vivo*, we designed a viral-based approach to disrupt DAR/NMDAR heteromers in a time-controlled manner owing to a doxycycline-dependent promoter. We found that the disruption of the D1R/NMDAR interaction in the NAc blocks cocaine-induced ERK activation and abrogates the development of both psychomotor sensitization and cocaine conditioned place preference (CPP), whereas the blockade of D2R/NMDAR interaction interferes with the maintenance of psychomotor sensitization and cocaine CPP. This work identifies DAR/NMDAR heteromers as molecular targets with a therapeutic potential not only in addiction but also for the numerous psychiatric disorders associated with an imbalance of DA and Glu transmission.

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Nanosymposium

453. Effects of Cocaine Use

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Topic: G.08. Drugs of Abuse and Addiction

Support: Center on Compulsive Behaviors via NIH Director's Challenge Award ZIA-AA000421

Title: Cocaine actions on cortico-striatal circuitry: A focus on cholinergic interneurons

Authors: *M. E. AUTHEMENT, J. SHIN, V. A. ALVAREZ;
Lab. on Neurobio. of Compulsive Behaviors, Natl. Inst. on Alcohol Abuse and Alcoholism, Bethesda, MD

Abstract: Cholinergic interneurons (CINs) of the striatum are thought to play a critical role in behavioral flexibility and dysfunciton of CINs may underlie the pathology of compulsive behaviors that are expressed in drug abuse. Although CINs account for only 1% of striatal neurons, they are the major source of acetylcholine in the striatum. Recent studies have identified another critical function of CINs: triggering dopamine release. Direct and indirect activation of CINs through cortical and thalamic inputs can evoke dopamine release independent of midbrain dopaminergic neuron firing. Therefore, we hypothesize that if drugs of abuse have effects on CIN physiology, they would affect this novel form of striatal dopamine signaling. The central goal of this study is to identify the mechanisms underlying the acute and chronic effects of cocaine, a stimulant drug of abuse, on CIN activity and on synaptic inputs to CINs. We focus on glutamatergic inputs from the prefrontal cortex (PFC) onto CINs based on the well-known role of the PFC in behavioral flexibility and inhibitory control. Recordings from CINs in *ex vivo* brain slices showed that cocaine potently and dose-dependently depressed glutamatergic transmission from PFC inputs. The mechanism underlying this acute depression appeared to be presynaptic. Cocaine increased the spontaneous action potential firing in CINs by two-fold. and this effect was blocked with both a serotonin and D1/D5 dopamine receptor antagonist. Following repeated cocaine administration, the CIN excitability was decreased. Thus, while cocaine acutely increases CIN firing, chronic exposure to cocaine produces a long-lasting depression of firing. These studies are revealing novel actions of cocaine on cortico-striatal circuitry that we speculate may contribute to the loss of inhibitory control and behavioral flexibility that characterize compulsive cocaine use.

Disclosures: M.E. Authement: None. **J. Shin:** None. **V.A. Alvarez:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

Location: Room S405

Time: Tuesday, October 22, 2019, 8:00 AM - 10:15 AM

Presentation Number: 454.01

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant HD079518

Title: Longitudinal changes in hippocampal subfield volume predict improvements in memory ability during early to mid-childhood

Authors: *K. L. CANADA[1], F. GENG[2], T. RIGGINS[1];
[1]Psychology, Univ. of Maryland, College Park, MD; [2]Dept. of Curriculum and Learning Sci., Zhejiang University, Xixi Campus, Hangzhou, China

Abstract: Early childhood is a time of rapid, significant change in memory abilities. Prior research has linked gains in memory to the hippocampus, a heterogeneous subcortical structure consisting of the dentate gyrus (DG), cornu ammonis (CA) 1-4, and the subiculum (Sub). Yet, currently lacking is a detailed understanding of the developmental trajectory of these subfields during early childhood and their relations to different aspects of memory. We tested the hypotheses that 1) subfields will show distinct developmental trajectories from early to mid-childhood and 2) that these subfields will predict distinct measures of memory.

We examined longitudinal changes in children's subfield volumes and memory ability between 4-8 years utilizing an accelerated longitudinal design. The preliminary sample for this study includes 81 participants (43 males) with 186 structural MRI scans (39 had three scans, 27 had two scans, and 15 had one scan). For memory measures, 74 participants provided data at all time points and 7 at two time points. To assess memory, participants learned a set of 12 novel facts, 6 each from two different sources. Approximately one week later, participants were tested on their memory for both facts and their sources. Measures of total fact memory and source memory contingent on correct fact memory (i.e., conditionalized source memory) were derived. To assess age-related changes in subfield volumes in hippocampal head and body, memory, and relations between subfields and memory, we utilized linear mixed effects models and formal model-fitting procedures. Sex effects were added to the best-fitting models and model fit was tested for improvement.

Preliminary results showed non-linear patterns for total fact memory and conditionalized source memory, with sharp increases starting after age 4 that slowed near age 7. Sex did not improve model fit. Heterogeneity was observed in subfield development: for volume in the head CA2-4/DG did not change with age ($p > 0.05$), while CA1 increased ($p = 0.016$) and Sub decreased ($p = 0.044$). In hippocampal body, CA2-4/DG, CA1, and Sub volume increased from early childhood into mid-childhood *(ps* < .03*)*, although the degree of change varied. Main effects of sex improved fit in all models except CA2-4/DG and CA1 in the body. Changes in total fact memory related to increases in CA2-4/DG and decreases in CA1 in body. Changes in conditionalized source memory related to increases in CA2-4/DG in body.

In summary, hippocampal subfields show differential volumetric changes from early to mid-childhood. These volumetric changes contributed to specific improvements in memory, with subfields selectively contributing to increased memory abilities.

Disclosures: K.L. Canada: None. **F. Geng:** None. **T. Riggins:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

Location: Room S405

Time: Tuesday, October 22, 2019, 8:00 AM - 10:15 AM

Presentation Number: 454.02

Topic: H.02. Human Cognition and Behavior

Title: Neural mechanisms of episodic memory and the influence of schooling - A longitudinal study

Authors: *S. NOLDEN[1], G. BROD[2], Y. SHING[1];
[1]Goethe-University Frankfurt am Main, Frankfurt am Main, Germany; [2]Leibniz Inst. for Res. and Information in Educ. (DIPF), Frankfurt am Main, Germany

Abstract: The so-called “5-7 shift” describes the remarkable improvements that are broadly observed in children’s cognitive abilities across five to seven years of age. Coinciding in time with school entry for most children living in modern societies, it is unclear to what extent the “5-7 shift” is driven by exposure to formal schooling. Furthermore, the effects of formal schooling on brain development are poorly understood. In this longitudinal study, we investigated if schooling acts as a catalyst of maturation, possibly by pushing forward progressions in cognitive and brain development generally. We tested 41 5-year-old children who were born shortly before or after the official cutoff date for entry into first grade. At the first time point of measurement, all children were still attending kindergarten. About one year later, the children were tested again. At this second time point of measurement, 15 children experienced their first year of schooling (first graders, n = 15, 8 female, mean age at baseline = 5.5 years, mean age at follow up = 6.5 years), and 26 remained in kindergarten (kindergarteners, n = 26, 12 female, mean age at baseline = 5.3 years, mean age at follow up = 6.4 years). Using an fMRI task that assessed incidental memory for indoor and outdoor scenes, we found that children in this age range relied strongly on the medial temporal lobe (MTL) but not at all on the prefrontal cortex (PFC) for forming memory representations (remembered vs. forgotten trials, subsequent memory effect). This stands in contrast to the existing literature with older children and adults who typically show strong subsequent memory effect in both MTL and PFC. Both children groups improved equally in their memory performance across one year, but there were no longitudinal changes nor group by time interaction in neural activation in either MTL nor PFC. Sex differences were not assessed. We conclude that subsequent memory effect between five to six years of age relies heavily on the MTL but not PFC, and schooling as an experience may not sculpt children’s neural memory networks in a general fashion during the transition from preschool to first grade.

Disclosures: S. Nolden: None. **G. Brod:** None. **Y. Shing:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

Location: Room S405

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Presentation Number: 454.03

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1633873

Title: The relationship between age, retrieval-related hippocampal activity, and cortical reinstatement

Authors: *P. F. HILL, M. D. RUGG;
Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX

Abstract: Patterns of cortical activity elicited during recollection overlap with patterns elicited by the initial experience of the recollected event ('cortical reinstatement'), and this retrieval-related activity is held to represent the 'content' of recollection. It has been proposed that the hippocampus is responsible for both enabling cortical reinstatement, and mediating the relationship between reinstatement and memory performance. Hence, differences in the strength of this relationship may contribute to age-related differences in recollection accuracy. Here, young and older adults (Ns = 24) underwent fMRI as they studied concrete nouns paired with images of faces or scenes. Old and new words were presented in a later memory test and, for words judged 'old', a source memory judgement for the corresponding image class was required. Using multivariate pattern similarity analyses, item-level cortical reinstatement was defined as the difference between the mean across-voxel correlation between study-test trial pairs comprising the same items, and the mean correlation between all other study-test pairs involving the same image class. To examine the link between hippocampal activity and cortical reinstatement, fMRI data were submitted to a GLM to estimate retrieval-related hippocampal BOLD responses for individual trials. Fisher transformed correlation coefficients between single-trial hippocampal activity and pattern similarity were determined for each participant and submitted to group-level *t*-tests (two-tailed). For scenes, the mean correlations between pattern similarity and left hippocampal activity were significantly greater in young compared to older adults, and the magnitude of this relationship was significantly different from zero in young adults only. For faces, correlations were not significantly different from zero in either age group, and did not differ between the two groups. For both image classes, the magnitude of the relationship between left hippocampal activity and pattern similarity predicted source memory performance independently of age (faces partial $r = .59$, $p < .001$; scenes partial $r = .33$, $p = .024$). These findings suggest that recollection accuracy may depend, in part, on hippocampally-mediated reinstatement of details idiosyncratic to a specific study event, and that this dependence is not moderated by age.

Disclosures: **P.F. Hill:** None. **M.D. Rugg:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

Location: Room S405

Time: Tuesday, October 22, 2019, 8:00 AM - 10:15 AM

Presentation Number: 454.04

Topic: H.02. Human Cognition and Behavior

Support: Johns Hopkins University Department of Neurology internal funds

Title: Neural correlates of self-referential memory encoding in development

Authors: R. LAWRENCE, J. CHENG, M. EUSTACHE, P. OURAND, ***X. J. CHAI**;
Johns Hopkins Univ., Baltimore, MD

Abstract: Information that is encoded in relation to the self tends to be better remembered. This self-referential effect of memory has been previously shown in adults and in children. Our study investigated the development of neural correlates of self-referential encoding in a group of children (7-12 years of age, N = 45) and a group of young adults (18-25 years of age, N= 35). Participants viewed pictures of color objects displayed on a background image while inside the MRI scanner and answered either a self-referential question (Do you like the object?) or a semantic question (Is the object a living thing?) for each object. Behavioral results demonstrated clear memory facilitation of self-referential encoding compared to semantic encoding. Both the object itself (item memory) and the background image (source information) were better remembered when encoded in the self-referential condition. This effect holds for both children and the adult group. Adults had greater memory scores than children for both self-referential and semantic encoding, but the group difference was greater for self-referential encoding. Self-referential encoding, compared to semantic encoding, activated regions of the default network including medial prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex, and bilateral inferior frontal cortex (IFC) in adults. In children, self-referential encoding activated the medial prefrontal cortex. Compared to children, adults showed greater activations in dorsal medial prefrontal cortex, precuneus, left angular gyrus and right inferior frontal gyrus. These results suggest that self-referential encoding may contribute to memory performance differences between children and adults, and that the brain regions mediating self-referential encoding, including part of default network, are still developing from late childhood into young adulthood.

Disclosures: **R. Lawrence:** None. **J. Cheng:** None. **M. Eustache:** None. **P. Ourand:** None. **X.J. Chai:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

Location: Room S405

Time: Tuesday, October 22, 2019, 8:00 AM - 10:15 AM

Presentation Number: 454.05

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH107512
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Title: Medial temporal and frontotemporal theta rhythms predict subsequent memory in the developing brain

Authors: *E. JOHNSON[1,2], Q. YIN[2], L. TANG[2], E. ASANO[3], N. OFEN[2];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Wayne State Univ., Detroit, MI; [3]Pediatric Neurol., Children's Hosp. Michigan, Wayne State Univ., Detroit, MI

Abstract: Although children as young as 4-6 years of age do form memories of events in their own lives, it is widely understood that declarative memory continues to improve into young adulthood. Indeed, memory development follows a protracted trajectory concomitant with the maturation of cortical and cortico-hippocampal connections, but the mechanisms by which these networks support memory in children are not known. Nineteen subjects (5.9-20.5 years) undergoing direct cortical monitoring (ECoG) made indoor/outdoor judgements of pictures of scenes in preparation for a recognition test. We hypothesized that medial temporal (MTL) theta rhythms, which are associated with memory in adults and animal models, would predict subsequent memory in children. Theta time-series were calculated for each 3-s encoding trial in all MTL channels (n = 75) at a per-subject theta-range frequency (6.9 ± 1.1 Hz, mean ± SD) using the Hilbert-bandpass technique, and then z-scored on the pretrial baseline using statistical bootstrapping. We observed increased theta power with presentation of each scene and a negative subsequent memory effect, such that increases in theta power were greater for subsequently forgotten compared to remembered scenes around the indoor/outdoor response. The subsequent memory effect was independent of age. Next, we investigated whether theta rhythms supported connectivity between the MTL and prefrontal cortex (PFC; n = 325 channels) during memory formation. Spectral decomposition was performed between 1-20 Hz using a Hanning taper and frequency-dependent sliding window. MTL-PFC coherence peaked in the theta band (~7 Hz) and sub-second deviations in theta directional connectivity predicted memory formation. We observed a shift in direction over time such that MTL led PFC during the initial 1 s of scene viewing and PFC led MTL after the indoor/outdoor response. Furthermore, individual differences during the initial 1 s of scene viewing demonstrated a double-dissociation in the network-level predictors of successful memory formation by age. Top performing adolescents showed PFC leads during the initial 1 s of scene viewing, whereas performance was lowest among children who showed PFC leads during the initial 1 s of scene viewing. Our findings reveal that theta rhythms dictate memory formation with sub-second temporal precision, even in children, and suggest how MTL-PFC network maturation partially explains developmental gains in memory.

Disclosures: **E. Johnson:** None. **Q. Yin:** None. **L. Tang:** None. **E. Asano:** None. **N. Ofen:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

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Topic: H.02. Human Cognition and Behavior

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NSF GRFP

Title: Network analysis of memory and attention networks in the brain

Authors: ***M. BOTDORF**[1], F. GENG[2], T. RIGGINS[3];
[1]Psychology, Univ. of Maryland, Col. Park, College Park, MD; [2]Col. of Educ., Zhejiang Univ., Hangzhou, China; [3]Psychology, Univ. of Maryland, College Park, MD

Abstract: In adults and children, episodic memory relies on a network of brain regions (EMN; episodic memory network), including the hippocampus and various cortical regions (Vincent et al., 2006). Recent research suggests that prefrontal regions included within the frontoparietal attention network (FPN) are also important for the development of memory (Tang et al., 2018). However, differences between children and adults in functional connectivity of the EMN and FPN and how development of these networks relate to episodic memory in young children is unclear.

The present study used graph theoretical and functional connectivity analyses to investigate differences in the density and strength of functional associations within and between EMN and FPN in children and adults. Given the importance of the EMN, this study also examined relations between functional connectivity within EMN and memory performance in children. A total of 137 4- to 8-year-old children and 30 adults were included in the study. Both adults and children completed a structural MRI scan and a task-free fMRI scan (Vanderwal et al., 2015), and children completed an Ordered Recall Task (Bauer et al., 2013) outside the scanner.

Results revealed similar network structure in adults and children. Specifically, analyses assessing density of functional connections showed that modularity did not differ between the two groups, $F(1,161) = 2.32$, $p = 0.13$. This suggests that connection density within versus between networks is similar children and adults. Analyses assessing connectivity strength showed stronger connectivity both within and between networks in adults compared to children. Further analyses focused on the hippocampus in relation to memory showed a significant interaction between age and strength of hippocampal-EMN connections ($b = 0.45$, $SE = 0.19$, $p = 0.03$) in children. Specifically, functional connectivity was positively related to memory performance in older, but not younger children. All associations held after controlling for effects of age, sex, and motion.

These findings suggest similar EMN-FPN structure in adults and children, although connectivity within and between networks is stronger in adults. This supports research suggesting that brain and cognitive development in children may be better characterized by the refinement of connections versus widespread changes in network organization (de Bie et al., 2012). Results also suggest that connectivity within the EMN is important for memory performance specifically in older children. Overall, these results have important implications for the study of memory development, an ability that is integral to learning in early childhood.

Disclosures: M. Botdorf: None. **F. Geng:** None. **T. Riggins:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

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Presentation Number: 454.07

Topic: H.02. Human Cognition and Behavior

Support: Jacobs Foundation

Title: Income-related differences in reward anticipation-mediated memory enhancement in children

Authors: *L. MEINE[1], A. KERESZTES[2,3,4], L. RAFFINGTON[5], C. HEIM[6,7], Y. SHING[8,3]; [1]Inst. of Psychology, Johannes Gutenberg-Universität Mainz, Mainz, Germany; [2]Res. Ctr. for Natural Sci., Hungarian Acad. of Sci., Budapest, Hungary; [3]Ctr. for Lifespan Psychology, Max Planck Inst. for Human Develop., Berlin, Germany; [4]Fac. of Educ. and Psychology, Eotvos Lorand Univ., Budapest, Hungary; [5]Population Res. Ctr., Univ. of Texas at Austin, Austin, TX; [6]Inst. of Med. Psychology, Charité-University Medicine, Med. Ctr., Berlin, Germany; [7]Dept. of Biobehavioral Hlth., Pennsylvania State Univ., University Park, PA; [8]Inst. of Psychology, Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Anticipation of reward has been shown to enhance incidental encoding of episodic memories. Neuroimaging evidence suggests that this memory-enhancement is partly driven by modulated interactions between the medial temporal lobe and the dopaminergic midbrain. Yet, developmental changes in memory and reward system functioning as well as their susceptibility to environmental effects, such as socioeconomic disadvantage and stress, are poorly understood. This study investigated socioeconomic- and stress-related differences in the memory-enhancing effect of reward anticipation in a sample of 76 children aged 6-7 years. We examined reward and memory processing using functional magnetic resonance imaging (fMRI). Following Wittmann et al. (2005), in each trial, participants saw a unique picture from one of two object categories (living vs. non-living) followed by a number comparison task. Object category served as a cue for whether a correct response on the number comparison task would or would not be rewarded.

Recognition memory for the unique pictures was subsequently tested outside the scanner. Stress was assessed through parent's self-reported stress. In addition, associations with children's hair cortisol levels, which may be affected by chronic stress exposure, were explored. Consistent with previous research, reward anticipation enhanced episodic memory performance (Likelihood ratio test $\Delta X^2(1)=11.463$, $p<0.001$), increasing memory accuracy by 7% ± 2% (standard errors). Interestingly, the magnitude of this effect was modulated by family income as evidenced by a significant interaction effect of income x reward condition on recognition performance (Likelihood ratio test $\Delta X^2(1)=4.18, p<0.05$). Anticipation of reward particularly enhanced correct recognition in children from lower income families. No such modulatory effects were found for self-reported stress or hair cortisol levels. Our results extend research on reward and memory interactions to a younger age group and highlight differential effects driven by family income. Further analyses are ongoing to examine the neural correlates of reward anticipation-mediated memory enhancement and to investigate how these are modulated by family income. Using a region-of-interest approach, analyses will focus on medial temporal lobe (particularly the hippocampus) and midbrain structures.

Disclosures: L. Meine: None. **A. Keresztes:** None. **L. Raffington:** None. **C. Heim:** None. **Y. Shing:** None.

Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

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Topic: H.02. Human Cognition and Behavior

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Title: Direct brain recordings reveal the involvement of the occipital cortex in memory formation in children

Authors: *Q. YIN[1], E. L. JOHNSON[1,2], L. TANG[1], K. I. AUGUSTE[3,4], R. T. KNIGHT[2], E. ASANO[1,5], N. OFEN[1,6];
[1]Wayne State Univ., Detroit, MI; [2]Univ. of California, Berkeley, CA; [3]Univ. of California, San Francisco, CA; [4]UCSF Benioff Children's Hosp., Oakland and San Francisco, CA; [5]Children's Hosp. of Michigan, Detroit, MI; [6]Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Maturation of high-level visual regions is associated with developmental gains in the encoding of complex visual stimuli. However, it is unknown whether low-level visual processing in the occipital cortex supports age-related gains in memory for complex visual stimuli. Alpha

rhythms are the most prominent feature in occipital regions and have been shown to support visual processing. We provide rare intracranial evidence from 20 subjects (6.2-20.5 years) undergoing direct cortical monitoring (ECoG), which indicates that occipital alpha rhythms during visual processing support memory formation in children. Subjects studied pictures of scenes in preparation for a recognition test. Scenes were classified as high- or low-complexity by the number of unique object categories depicted. Recognition accuracy for high-complexity, but not low-complexity, scenes increased with age. Time-frequency representations of power from 5-20 Hz were calculated using a Hanning taper for each 3-s scene encoding trial, z-scored on a 300-ms pre-stimulus baseline via statistical bootstrapping. Group-level analyses used linear mixed-effects models and ANCOVA. Task-induced alpha increases were lower for viewing high-complexity compared to low-complexity scenes, and the magnitude of these negative complexity effects increased with age. Critically, children who displayed greater recognition accuracy for high-complexity scenes had lower task-induced alpha increases during the first 1 s of high-complexity scene viewing compared to those who had lower recognition accuracy. Furthermore, negative subsequent memory effects were observed throughout the scene presentation period, such that task-induced alpha increases were lower for subsequently remembered scenes compared to forgotten scenes, revealing an occipital cortex predictor of subsequent memory. Finally, individual differences during the second 1 s of high-complexity scene viewing demonstrated a double-dissociation in the predictors of recognition accuracy by age. We found that negative subsequent memory effects were increased in children who displayed greater recognition accuracy, while the opposite pattern was observed in adolescents. These results reveal age differences in the involvement of the occipital cortex during the encoding of complex scenes, partially explaining age-related gains in memory. Furthermore, these results suggest that increased low-level visual processing of complex visual scenes allows children to more successfully encode complex visual scenes. More broadly, our findings demonstrate that the occipital cortex supports memory formation for visual scenes in children.

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Nanosymposium

454. Medial Temporal Lobe in Learning and Memory During Development

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Topic: H.02. Human Cognition and Behavior

Support: NIH grant MH091109

Title: Longitudinal changes of hippocampal subfields predict memory improvements at the transition into adolescence

Authors: E. JOHNSON, Y. FANDAKOVA, J. LEE, ***S. G. GHETTI**;
Univ. for California, Dav, Davis, CA

Abstract: Introduction. Episodic memory, the capacity to remember past events with rich detail, improves markedly from middle childhood into adolescence (Ghetti & Bunge, 2012). However, relatively little is known about how changes in relevant neural circuitry support these behavioral improvements. We completed a longitudinal study of hippocampal development given the long-held, but untested, hypothesis that this structure reaches maturity in early childhood, which contrasts recent evidence from cross-sectional studies. Developmental differences in the hippocampus may manifest in structural changes in the relative size of hippocampal subfields (i.e., CA3/DG relative to CA1 and subiculum). Hypotheses. We tested the hypotheses that there would be distinct developmental trajectories CA3DG and CA1 relative to subiculum and that these regions would distinctively predict memory changes over time.Study Population, Methods and Results. To date, we examined volumetric changes in hippocampal subfields in 134 participants across 3 time points (Mage at T1= 9.45 years; Mage at T2= 10.86 years, Mage at T3 = 12.12 years; 252 total scans). Participants learned and retrieved associations between items and scenes. Using mixed level models, we found a significant interaction between change in age and hippocampal subfield, such that compared to the subiculum, both CA1 and CA3DG increased in volume over time (ps <.001). Preliminary analyses showed that changes in CA3DG predicted increases in memory accuracy over time (<.05). Additional analyses will examine if changes in puberty levels moderate these findings, and whether these longitudinal associations are replicated across additional memory tasks available in this sample. Conclusions. Structural changes in the hippocampus occur between middle childhood and adolescence and these changes are important for behavioral improvements during this period. Initial evidence also point to the role of pubertal changes might in explaining developmental trajectories.

Disclosures: E. Johnson: None. **Y. Fandakova:** None. **J. Lee:** None. **S.G. Ghetti:** None.

Nanosymposium

455. Working Memory: Mechanisms I

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Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China Grant 31571115
Beijing Municipal Science & Technology Commission Grant Z181100001518002

Title: Temporal manipulation of memory reactivations in humans

Authors: *J. LI[1], Q. HUANG[2], H. LUO[2];
[2]Sch. of Psychological and Cognitive Sci., [1]Peking Univ., Beijing, China

Abstract: Storing temporal sequences of events is fundamental to many cognitive functions, such as language, episodic memory, movement control, and decision making. Recent studies demonstrated that the representation of multiple items in working memory is mediated by serial reactivations during the delay period, yet the causal evidence is still lacking. Here we develop a "behavioral temporal interference" approach to disturb and manipulate the item-specific replay during retention when participants performed a sequence memory task. The results from eight experiments consistently demonstrate that this behavioral approach successfully alters sequence memory behavior. When items are reactivated synchronously so that they could not replay in a time-dissociated way, the serial position effect (SPE), a typical behavioral index of sequence memory, is disrupted. Reversing the replay order during retention also changes SPE, suggesting that the temporal order of reactivations is essential as well. Our results provide causal evidence supporting the relationship between the sequential reactivations during retention and sequence memory behavior, and suggest a promising and efficient behavioral approach to manipulate the temporal structure of multiple items held in working memory.

Disclosures: J. Li: None. **Q. Huang:** None. **H. Luo:** None.

Nanosymposium

455. Working Memory: Mechanisms I

Location: Room S104

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Presentation Number: 455.02

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust
British Academy

Title: Tracking the item in focus of attention in working memory through pupillometry

Authors: *N. ZOKAEI[1], A. BOARD[1], S. G. MANOHAR[2], A. NOBRE[1];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Dept. of Exptl. Psychology, Oxford, United Kingdom

Abstract: Studies have shown that pupil responses can reveal the nature of attended information at perception. We, in a series of studies, asked whether pupillary responses also reflect the item in the focus of attention during working memory retention. In each study, participants were asked to keep in mind the orientation of two gratings, one bright and one dark. At the end of the trial, a probe stimulus prompted reproducing the orientation of one of the stimuli. Importantly, there was no difference in the brightness of the anticipated probe. We manipulated the item in the focus of attention using auditory retrospective cues; cueing either the brightness (study 1) or the location (study 2) of one of the stimuli or using internally guided temporal expectations to prioritise individual's items in memory at specific times during the delay interval (study 3).

Our findings demonstrated that the pupils reflected the item in focus of the attention during a blank memory delay, with prioritised darker stimuli eliciting a larger pupil response compared to bright stimuli. Importantly, the same pupil response was observed even when brightness was an irrelevant feature of the stimuli and could be ignored (study 2 and 3, as the spatial location of the most relevant item was cued). This suggest, to some extent, preservation of irrelevant features in working memory representations, including brightness which can be tracked via the pupil response. Lastly, our findings from study 3 demonstrate that the pupil response to the memory representations can be dynamically modulated by internally guided temporal expectations. Complementing these theoretical advances, our results also carry an important practical implication. A thought-provoking corollary to our finding is that pupils provide a reliable measure of what is in the focus of mind, thereby offering a highly sensitive, non-invasive and real-time manner to track the objects of thought.

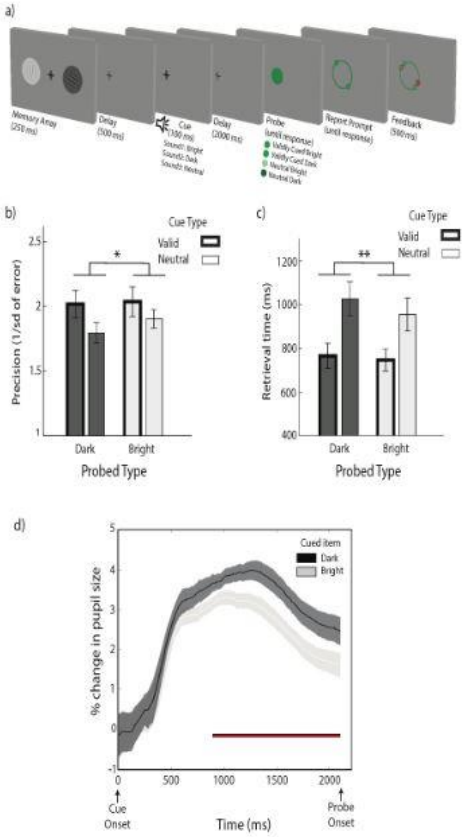

Figure 1. Experiment 1 task schematic and behavioural results. **a)** During encoding, participants were presented with two randomly oriented gratings, in dark or right grey and were asked to keep in mind their orientations. During memory delay, an auditory sound either cued the participants to bright or dark grating (100% valid) or was uninformative of the upcoming probe. This was followed by a delay before the presentation of the probe. After the probe appeared, participants first had to retrieve the item from working memory and then report the exact orientation of the probed grating. **b)** Mean precision as a function of the probed item's brightness (bright/dark) and cue type (valid/neutral). **c)** Mean retrieval time as a function of probe item's brightness and cue type. **d)** The influence of cue on pupil diameter. Comparisons of these traces with each other and against zero are shown. Validly cued darker gratings elicited a larger change in pupil size compared to validly cued brighter gratings. The shaded area indicates the standard error within subjects. Error bars indicate SEM, calculated across participants. * $p<0.05$ and ** $p<0.005$.

Disclosures: **N. Zokaei:** None. **A. Board:** None. **S.G. Manohar:** None. **A. Nobre:** None.

Nanosymposium

455. Working Memory: Mechanisms I

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Institute of Information & Communications Technology Planning & Evaluation(IITP) grant funded by the Korea government (MSIT) (No.2019-0-01371, Development of brain-inspired AI with human-like intelligence)

Title: Localized attentional-modulation of prefrontal cortex activity in response to implicitly-presented emotional stimuli

Authors: *H. SONG, S. LEE;
Dept. of Bio and Brain Engin., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The prefrontal cortex (PFC) is known to play an important role in executive function, top-down cognitive processing, and attention. Past findings show that these cognitive abilities can be disrupted by emotional stimuli, often implicitly, in the absence of one's awareness. In this study, we aimed to test the effects of several types of implicit emotional visual stimuli on attention and PFC activation. To do this, we presented positively-valenced, negatively-valenced, and sexually-arousing pictures (from the International Affective Picture System), both explicitly or masked implicitly, to subjects immediately before they performed the Attention Network Task (ANT). On each trial, we measured hemodynamic response in the PFC using high-density functional Near-infrared Spectroscopy (fNIRS).Our results show differences in both localization and attention-modulation across the three implicit emotion conditions. The right medial PFC (mPFC) activity was positively correlated with attention in the negative-implicit condition ($r=0.76$, $p=0.01$) but negatively correlated with attention level in positive-implicit condition ($r=-0.71$, $p=0.02$). The sexual-implicit condition showed a negative correlation between left dorsolateral PFC (dlPFC) activity and attention ($r=-0.74$, $p=0.01$). Interestingly, attentional performance was significantly impaired solely in the sexual-implicit condition. These findings add to the existing literature on the differential effects of emotional valence on attention-related mechanisms in the brain. An active mPFC in response to implicit negative stimuli associated with better attention (in the task) may reflect emotional regulation through the mPFC-amygdala circuitry. On the other hand, activation of the mPFC in the positive condition may result in the

opposite effect if implicit positive emotions enhance attention. Furthermore, we reveal that subjects have lowered attention in response to sexually-arousing implicit stimuli when the dlPFC activity is high. Given the vulnerability of attention in THE sexual-implicit condition, the distraction-elicited dlPFC activity in response to briefly presented (67ms) sexually-arousing pictures may predict lower task-related attention. This interpretation, however, would need further exploration in future studies. Ultimately, we hope that this study will give insight to diverse situations in which temporary implicit distractions due to emotional arousal and its effects on the brain could potentially be dangerous or critical for quick decisions.

Disclosures: H. Song: None. **S. Lee:** None.

Nanosymposium

455. Working Memory: Mechanisms I

Location: Room S104

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Presentation Number: 455.04

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH064498

Title: Rotational remapping as a candidate mechanism for priority-based recoding in visual working memory: Empirical and computational evidence

Authors: *Q. WAN[1], Y. CAI[2], J. SAMAHA[3], T. T. ROGERS[1], B. R. POSTLE[1];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Beijing Normal Univ., Beijing, China; [3]Univ. of California, Santa Cruz, Santa Cruz, CA

Abstract: We recorded EEG while male and female young adult humans performed a 2-back working memory (WM) task with oriented grating stimuli, to track the transition of the neural representation of an item ("*n*") from its initial encoding, to a status of "unprioritized memory item" (UMI, while *n + 1* was compared to *n - 1*), then back to "prioritized memory item" (PMI, for comparison against *n + 2*). Analysis with multivariate inverted encoding modeling (IEM) suggested a change of representational format as a function of priority: the neural representation of the UMI was rotated by 90° relative to its representation when a PMI. To determine whether this recoding operation was sensitive to the orientation of the other item concurrently in WM (i.e., to *n - 1*), we divided the data based on the angular difference between the orientations of concurrent UMI and PMI and reconstructed the IEMs separately for each. This revealed no evidence for a systematic interaction between the recoding of the UMI and the concurrent PMI. To gain more insight about the mechanisms underlying priority-based recoding, we trained a simple recurrent network (SRN) to perform the 2-back task: backpropagation was employed to reduce the sum of squared errors across 10,000 training epochs, each comprising 50 different sequences of 20 stimulus presentations across 58 steps. The trained SRN, when given 10 novel

sequences, performed at 93% correct, comparable to humans. We interrogated the hidden layer of the SRN by using multidimensional scaling (MDS) to visualize the 10D stimulus representations during the ISI. The hidden layer represented the PMI in orientation-specific clusters, each occupying a discrete manifold, such that orientation varied systematically along one axis. Although the UMI was also represented along similarly discrete manifolds, with the distances between orientations preserved, the axis of orientation was orthogonal to that of the PMI. These simulated results recapitulate the representational transformation observed in the EEG data, and can also explain fMRI results presented elsewhere by our group and by others. Priority-based recoding may be implemented as a rotational remapping that is emergent from the dynamics of high-dimensional distributed representations.

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Nanosymposium

455. Working Memory: Mechanisms I

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Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH087214
ONR N00014-15-1-2790
F32 MH115597

Title: Concurrent fluctuations of attention and working memory

Authors: *M. T. DEBETTENCOURT, P. A. KEENE, E. AWH, E. K. VOGEL;
Univ. of Chicago, Chicago, IL

Abstract: The intricate relationship between attention and working memory has been typically explored in the aggregate. Attention and working memory are clearly intertwined, as shown by covariations in individual ability and their recruitment of similar neural substrates. However, this aggregate relationship does not necessarily presuppose anything about the moment-to-moment relationship between attention and working memory. In this work, we leveraged the fact that both attention and working memory fluctuate over time, and behavioral and neural signals track these fluctuations. The goal of this study was to investigate the relationship between fluctuations in attention and working memory. We developed a novel hybrid task that interleaved a sustained attention to response task and a whole report working memory task. Throughout the study, participants were presented with multi-item shape displays. We manipulated the relevant feature across the tasks: shape for attention and color for working memory. The attention task was designed to encourage habitual responding, as participants had to repeatedly make the same

response. In Experiment 1, we established that trial-by-trial performance fluctuations were correlated across the attention and working memory tasks. Attention lapses correlated with worse working memory performance. In Experiment 2, we developed a real-time triggering procedure that monitored attention fluctuations to probe working memory during optimal (high attention) or suboptimal (low attention) moments. We demonstrated that when participants were attending less well, they stored fewer items in working memory. Follow up studies and pupil diameter data suggest these attention fluctuations were distinct from fluctuations of general task engagement. In Experiment 3, we delve into the neural basis of these attention fluctuations with EEG ERPs and oscillatory signals that track sustained spatial attention. Together, these studies provide insight into the synchronous and multifaceted relationship between attention and working memory fluctuations. We demonstrate that attention and working memory lapse together, providing new evidence for the tight integration of these cognitive processes.

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Nanosymposium

455. Working Memory: Mechanisms I

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NIH Grant R01-EY027925 (CEC and WJM)
NIH Grant R01-EY016407 (CEC)
Sloan Research Fellowship (TCS)

Title: Prioritized visual spatial working memory representations are maintained more precisely and with lower uncertainty

Authors: *T. C. SPRAGUE[1,3], H.-H. LI[1], A. H. YOO[1], M. RAHMATI[1], G. E. HALLENBECK[1], W. J. MA[1,2], C. E. CURTIS[1,2];
[1]Psychology, [2]Ctr. for Neural Sci., New York Univ., New York, NY; [3]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Increasing visual working memory (WM) load causes a steep decline in recall precision about specific feature values (Wilken & Ma, 2004; Zhang & Luck, 2008; Bays & Husain, 2008), and causes neural representations in visual, parietal, and frontal cortex to weaken (Buschman et al, 2011; Emrich et al, 2013; Sprague et al, 2014). However, knowledge about the relative importance of different items can enable the flexible allocation of resources to maintain the most relevant items most precisely, mitigating the impact of these bottlenecks (Griffin &

Nobre, 2013; Klyszejko et al, 2014; Emrich et al, 2017; Yoo et al, 2018). How this process of 'prioritizing' the most important information at the cost of less important information is implemented at a population level remains unknown. We hypothesized that prioritizing a WM representation sculpts its neural population response profile across entire retinotopic regions in visual, parietal, and frontal cortex, resulting in a representation that is read out more accurately and with reduced uncertainty (Ma et al, 2006; van Bergen et al, 2015). We scanned participants with fMRI while they performed a multi-item memory-guided saccade task. Participants precisely remembered two positions, each pre-cued with a different response probability, over an extended 12 s delay, then reported one cued position with a memory-guided saccade. The high/low priority item was queried on 66.7% vs 33.3% of trials, respectively. Participants effectively used the cued probabilities to prioritize items in WM: endpoints of memory-guided saccades were more precise for the high-priority item and responses were faster. To evaluate the impact of prioritization on neural representations, we extended a recently developed generative model based decoding approach (van Bergen et al, 2015) to estimate joint likelihood functions over the spatial positions of both items on a trial-by-trial basis. This allowed us to quantify the within-trial uncertainty with which each item was encoded in the population-level activation pattern. In visual field maps across occipital and parietal cortex, high-priority items were decoded with lower within-trial neural uncertainty and their positions were decoded with higher across-trial precision. Thus, the strategic allocation of WM resources sculpts the precision and uncertainty with which representations are encoded, revealing a key neural mechanism underlying voluntary control over memory quality.

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Nanosymposium

455. Working Memory: Mechanisms I

Location: Room S104

Time: Tuesday, October 22, 2019, 8:00 AM - 10:15 AM

Presentation Number: 455.07

Topic: H.02. Human Cognition and Behavior

Support: NIH MH063901

Title: Structural-functional relationships in prefrontal cortex for working memory

Authors: *J. A. MILLER[1], D. J. LURIE[2], K. WEINER[1], M. D'ESPOSITO[1];
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Abstract: The prefrontal cortex (PFC) is critical for higher-order cognition and shows sustained activity during working memory (WM), a core component of cognitive functioning (Leavitt, Mendoza-Halliday, & Martinez-Trujillo, 2017). However, structural-functional relationships in

human PFC remain largely underspecified because individual anatomical variability is poorly understood. For example, the patterning of tertiary sulci within the middle frontal gyrus has only recently been clarified (Petrides & Pandya, 2012). Here, we tested if tertiary sulci identified in individual subjects may serve as landmarks for functional activity during WM and PFC organization more broadly. Classic theories of frontal cortex function proposed that tertiary sulci, which emerge latest in gestation, should serve as landmarks in association cortex (Sanides, 1964), whereas modern theories of frontal cortex function have not considered such structure-function relationships (Badre & D'Esposito, 2009; Duncan, 2010).
To characterize anatomical landmarks, we manually labeled three sectors of the middle frontal sulcus (MFrS) in lateral PFC for 80 individual hemispheres from the Human Connectome Project guided by a recent definition of tertiary sulci within lateral PFC (Petrides & Pandya, 2012). We present three lines of evidence that the MFrS delineates structural and functional gradients for WM processes. First, we found that three distinct anatomical portions of the MFrS can be dissociated by *in-vivo* myeloarchitecture and resting-state network connectivity profiles. Second, using fMRI data during performance of a WM task (Rose et al., 2016), we found that the MFrS marks functional boundaries; functional activity was found along the MFrS in a different regional pattern when implementing attentional control during WM versus WM maintenance alone. This sustained MFrS WM activity was correlated with the strength of attentional modulation in visual cortex, indicative of the MFrS as a landmark for WM control processes. Lastly, we were able to functionally distinguish three components of the MFrS based on their particular engagement in cognitive processes. Each sulcal component contained different functional profiles that were derived from a model of meta-analytic fMRI data across 83 experimental task categories (Yeo et al., 2015). Overall, we demonstrate that the historically mischaracterized MFrS is not only a prominent landmark in individual subjects that is involved in WM, but is also comprised of three sectors that are anatomically and functionally distinct.

Disclosures: **J.A. Miller:** None. **D.J. Lurie:** None. **K. Weiner:** None. **M. D'Esposito:** None.

Nanosymposium

455. Working Memory: Mechanisms I

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Presentation Number: 455.08

Topic: H.02. Human Cognition and Behavior

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ERC Starting Grant ERC-639766

Title: Neonatal brain volume moderates the association between maternal sensitivity and working memory in toddlerhood

Authors: S. NOLVI[1], J. RASMUSSEN[2], A. GRAHAM[3], J. H. GILMORE[4], M. A. STYNER[5], *D. A. FAIR[6], S. ENTRINGER[1], P. WADHWA[7], C. BUSS[8];
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Abstract: Maternal sensitivity especially during the early stages of development with heightened neural plasticity is an important determinant of child development. Executive functioning (EF), in turn, lays a foundation for healthy cognitive and socio-emotional development, and can already be measured in early childhood. Total brain volume has been linked with better EF, but with typically small effect sizes, and animal research proposes that a larger brain might increase susceptibility to environmental influences. We therefore investigated whether neonatal brain volume constituted a neurophenotype of plasticity to the postnatal environment and moderated the association between maternal sensitivity and children's EF, specifically working memory and inhibitory control, in toddlerhood. The mother-child dyads (N = 47-51, 63% boys) from a longitudinal cohort at the University of California Irvine with following outcomes were included: a newborn MRI scan at M = 27.3 ± (SD) 13 days, maternal sensitivity assessment during free play at 6 months postpartum (M6), and child working memory (Spin the Pots) and inhibitory control (Snack Delay) assessment at M = 24.8 ± 0.9 months of age (M24). The primary interest was the interaction of total brain volume (residualized for gestational age and age at scan) by maternal sensitivity in predicting EF, and the models were adjusted for child sex, residuals of the intracranial volume, SES and age at testing. Larger neonatal brain volume moderated the association between maternal sensitivity and working memory at 24 months ($F_{47,6} = 10.34$, $p_{corr} = .006$, partial η^2 for the interaction term = .20), such that higher maternal sensitivity was associated with better working memory only for children with larger neonatal brain volume. No such effect was found for inhibitory control ($p_{corr} = .611$). The effect was not specific to grey or white matter volume. No sex differences were detected in the study. Our findings suggest that the effects of the postnatal caregiving environment on early childhood working memory specifically are conditioned, in part, upon characteristics of the newborn brain. Newborn total brain volume may represent a candidate neurophenotype reflecting interindividual differences in neuroplasticity that underlies sensitivity to environmental influences on emerging working memory skills. Ongoing analyses will consider additional domains of EF and the extent to which candidate neurophenotypes are unique or shared across domains.

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Nanosymposium

455. Working Memory: Mechanisms I

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Presentation Number: 455.09

Topic: H.02. Human Cognition and Behavior

Support: BBSRC

Title: Dynamical multiplexing of information during dual task performance in monkey prefrontal cortex

Authors: *D. F. WASMUHT[1], K. WATANABE[2], T. SUZUKI[3], M. G. STOKES[1];
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Abstract: Cognitive multitasking is limited by interference between component tasks. Neural substrates for such interference have been identified in the lateral prefrontal cortex (lPFC) mostly using univariate approaches. However, lPFC processes information in a dynamic, context dependent manner, possibly enabling multitasking during complex behaviour in the first place. We recorded from monkeys' lPFC while they simultaneously performed a spatial attention and working memory task (dual task). Monkeys learned to perform the dual task with a high success rate and over various levels of experimentally induced inter-task interference. Recorded neurons were tuned to unique task features as well as to complex mixtures of features from both tasks and time i.e. switching, linear-mixed and nonlinear-mixed selectivity. This heterogeneity in neural responses resulted in distinct patterns of activity across the population. Population activity patterns transitioned between distinct neural subspaces across task epochs, while protecting task specific representations from interference. Our data suggests that lPFC multiplexes information within and across tasks as well as time to achieve concurrent but distinct processing on the level of the population.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.01

Topic: I.03. Anatomical Methods

Support: Medical Research Council (MR/N01233X/1)
Wellcome Trust Strategic Award (104943/Z/14/Z)

Title: Thinking outside the box: A new role for hippocampal subfields in boundary extension

Authors: *A. N. WILLIAMS[1], M. POSTANS[1], C. J. HODGETTS[1], S. KUSMIA[1], R. LISSAMAN[1], D. HUCKER[2], J. ALLEN[2], A. D. LAWRENCE[1], K. S. GRAHAM[1];
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Abstract: Boundary extension (BE) is a memory error in which healthy participants construct an internal representation that extends beyond the borders of a scene. For instance, when two identical scenes are presented sequentially, participants will often indicate that the second scene appears closer-up than the first identical scene, suggesting that they have extended the scene borders of the initial presentation. This cognitive phenomenon is considered adaptive, facilitating the integration of discrete scene views into coherent spatial representations - a function thought to depend on the human hippocampus (Hodgetts et al., 2017; Zeidman & Maguire, 2016). While there is evidence that amnesic patients with reduced hippocampal volume exhibit reduced BE relative to controls, little is known about which of the various sub-regions (CA1, CA2, CA3, DG & subiculum) within the hippocampus might contribute to this phenomenon.
To address this question, we scanned 90 young adults using a 7T ultra-high-resolution imaging sequence with an effective in-plane resolution of 0.2 x 0.2 mm (aged 25-27 years, 44 female). This sequence allowed CA1, CA2, CA3, DG and subiculum to be structurally delineated along the whole hippocampus. Participants were recruited as part of a larger study, investigating genetics, scene perception, and memory. Outside the scanner, these participants undertook a rapid serial visual presentation BE task, in which pairs of identical scenes were presented sequentially (Mullally et al., 2012; De Luca et al., 2018). Participants were required to indicate whether, compared to the original scene, the second picture seemed closer-up, the same, or farther away.
A multiple regression model, taking account of intracranial volume, revealed that DG and CA3 volumes were predictors of BE (DG: $t(72) = 3.084$, $p = 0.003$, $\beta = 0.472$, $sr = 0.33$; CA3: $t(72) = 3.112$, $p = 0.003$, $\beta = -0.469$, $sr = -0.33$). Specifically, *larger* left CA3 volume and *smaller* left DG volume was associated with greater BE. These findings highlight a potential role for the DG and CA3 hippocampal subfields in online scene construction, consistent with imaging and neuropsychological work implicating the hippocampus in this memory phenomenon. This study provides novel insights into the hippocampal sub-regional contributions to boundary extension, and highlights the potential of 7T ultra-high-resolution imaging for refining existing models of human hippocampal function.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

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Presentation Number: 456.02

Topic: I.03. Anatomical Methods

Support: NIH/NIA Grant P50 AG008702

Title: Entorhinal cortex subfield volumes are differentially related to CSF AD biomarkers and memory in older adults without dementia

Authors: *L.-K. YEUNG[1], C. HALE[1], B. LAST[1], B. RIZVI[1], H. ANDREWS[2], R. P. SLOAN[3], L. S. HONIG[1], S. A. SMALL[1], A. M. BRICKMAN[1];
[1]Taub Inst., [2]Mailman Sch. of Publ. Hlth., [3]Neurol., Columbia Univ. Med. Ctr., New York, NY

Abstract: The entorhinal cortex (ERC) is the first cortical region where Alzheimer's disease (AD)-related neurodegeneration occurs. The ERC can be divided into anterolateral (alERC) and posteromedial (pmERC) subfields. Recent experimental work suggests these subfields may support distinct cognitive processes (e.g. Berron et al., 2018; Montchal et al., 2019; Reagh et al., 2018; Yeung et al., 2019, 2017). Furthermore, AD-related tau pathology appears earlier in lateral ERC compared to medial ERC (Braak and Braak, 1991). The present study investigated the relationship of alERC and pmERC volumes in older adults without dementia with cerebrospinal fluid (CSF) biomarkers of AD (i.e., beta amyloid, phospho-tau and total tau), and with memory, assessed with the ModRey, a list learning and memory test designed for preclinical populations. Both alERC and pmERC volumes were negatively related to CSF phospho-tau levels, but not with CSF amyloid levels. alERC volumes were positively related to recall, whereas pmERC volumes are negatively associated with intrusions. These data suggest that different kinds of memory change may reflect differences in AD-related neurodegeneration between the two ERC subfields at the earliest stages of AD progression.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.03

Topic: I.03. Anatomical Methods

Support: NIH R01 Grany MH074692

Title: Mnemonic prediction errors bias hippocampal states

Authors: *O. BEIN[1], K. D. DUNCAN[2], L. DAVACHI[3];
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[3]Psychology, Columbia Univ., New York, NY

Abstract: Mnemonic prediction errors arise when the experience does not match our internal predictions. In these situations, to promote an accurate and updated representation, it may be adaptive to upregulate the encoding of the novel information, while down-weighting retrieval of erroneous memory predictions. We adopted a 'state' approach to examining hippocampal functioning by leveraging recent empirical findings showing that during encoding of novel experiences, area CA1 may preferentially bias the processing of entorhinal cortical inputs while down-weighting memory retrieval processes thought to be supported by CA1 interactions with CA3. Thus, we hypothesized that mnemonic prediction errors should increase CA1-entorhinal connectivity and decrease CA1-CA3 connectivity. Human participants first extensively learned the identity, contents and layout of room stimuli. During fMRI scanning, participants were first verbally cued to retrieve learned rooms and were then presented either with an image of room identical to what was learned or with a modified version (with 1 - 4 changes) of that room. We found that CA1-entorhinal connectivity increased with the number of changes to the learned rooms. By contrast, CA1-CA3 connectivity significantly decreased as the number of changes increased. We additionally measured prediction strength in CA1 during the presentation of the verbal cue and found that, across participants, stronger predictions correlated with the CA1-entorhinal connectivity increase in response to violations. Our findings provide a putative mechanism by which prediction errors may drive memory updating - by biasing the hippocampus from a retrieval state to an encoding state, as reflected in the balance between CA1 connectivity with entorhinal cortex and CA3.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

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Topic: I.03. Anatomical Methods

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Title: Age differences in hippocampal glutamate modulation during object-location encoding: Evidence from proton functional magnetic resonance spectroscopy (1H fMRS)

Authors: *C. ANAND[1,2], R. HOMAYOUNI[3,2], Q. YU[3,2], S. RAMESH[2], D. KHATIB[1], C. DAHLE[2], J. A. STANLEY[1], N. RAZ[3,2];
[1]Psychiatry and Behavioral Neurosci., [2]Inst. of Gerontology, [3]Dept. of Psychology, Wayne State Univ., Detroit, MI

Abstract: Hippocampal glutamate is a key substrate of learning and memory, and glutamatergic dysfunction may signal age-related cognitive decline. The hippocampal subfields, abundant with glutamate receptors, exhibit age-related age differences in volume across the lifespan. We examined age differences in hippocampal glutamate modulation during encoding and retrieval of object-place associations, and its relation to the hippocampal subfield volumes. Proton functional magnetic resonance spectroscopy (^{1}H fMRS) was performed on unilateral hippocampi (randomized across subjects) of 14 young (25.8 ± 2.5 years old; 6 females) and 11 old (65.2 ± 2.9 years old; 5 females) participants during learning of object-place associations. The task included 12 cycles of encoding and retrieval, which were interspersed with epochs of counting backwards to prevent rehearsal. Gompertz function fitted to the associative learning data yielded three performance indicators: slope (learning rate), asymptote (maximum learning capacity), and inflection-point. . Epoch-wise glutamate levels were measured during a neutral condition (flashing checkerboard), as well as during encoding, and retrieval. Volumes of the dentate gyrus and CA3 (DG-CA3), CA1-2, subiculum, and entorhinal cortex (EC) were measured using a highly reliable manual tracing method. Older participants attained lower asymptotes, and tended to show a later inflection-point, compared to their young counterparts. The pattern of temporal changes in glutamate during association learning differed between age-groups, with age differences in levels of glutamate modulation noted only during encoding. Young adults showed increased glutamate levels during the first five blocks of encoding, with levels remaining high throughout encoding epochs. The older adults evidenced a complementary pattern: a decrease in glutamate during the first five blocks, and slow, tenuous ramping-up towards the end of encoding. In the young but not older participants, higher neutral-condition glutamate was linked to faster learning. Maximum glutamate levels during encoding corresponded to larger DG-CA3 and CA1-2 volumes in both age groups, with no associations observed for EC and subiculum. We conclude that glutamate modulation during memory encoding, observed *in vivo,* may underpin age-related memory decline and be differentially related to hippocampal subfield volumes. The advantage of fMRS in such investigations is that it allows assessment of the dynamics of a major neurotransmitter without confounding age differences in hemodynamics that limit the validity of fMRI inference.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

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Title: Impact of early estrogen deprivation on sleep, memory and hippocampal volume in middle-aged women

Authors: *N. GERVAIS[1], G. NICOLL[1], E. BAKER-SULLIVAN[1], C. LAUZON[1], L. MENDOZA[1], A. ALMEY[1], L. GRAVELSINS[1], A. BROWN[1], A. DUCHESNE[2], R. K. OLSEN[3], C. L. GRADY[4], G. EINSTEIN[1];
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Abstract: Sleep plays an essential role in promoting memory and hippocampal (HPC) structural integrity. Hormone deprivation following spontaneous menopause is associated with increased sleep and memory complaints. While greater sleep complaints are observed among women with early menopause due to bilateral salpingo-oophorectomy (BSO), no study has confirmed sleep disturbance (SD) using objective measures in this population. Additionally, few studies have examined the impact of BSO on memory and HPC structural integrity. Given the importance of sleep in maintaining memory and HPC structural integrity, an additional question is whether early hormone deprivation via BSO exacerbates poorer memory and HPC atrophy via SD. Our study aim was to determine if women with a BSO demonstrated greater SD, HPC atrophy, and poorer memory performance and if so, whether SD is related to reduced memory and HPC structural integrity. Estradiol-based hormone therapy (ET) has been shown to maintain memory, HPC structural integrity and sleep in spontaneously menopausal women and so an additional study aim was to examine whether women taking ET were protected against any adverse effects associated with BSO. Women with BSO either taking or not taking ET and premenopausal age-matched controls (AMC) were recruited. High resolution T2-weighted structural scans were obtained and volumes of HPC subfields quantified manually. Memory performance was assessed and both subjective and physiological sleep measures were collected. We found reduced working memory and scene recognition memory, smaller volume of the dentate gyrus, CA2 and CA3 subfields (DGCA23), and increased SD in the BSO group, but not the BSO+ET group. Poorer sleep was associated with smaller DGCA23 volume. This study underscores the adverse effects of early hormone loss on sleep, memory and HPC structural integrity, and suggests that SD associated with estradiol loss may contribute to selective reduction in HPC volume and memory.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

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R01AG054073
R01AG058537 (PI O'Bryant)

Title: Automated measurement of medial temporal lobe subregion cortical thickness using minimum line integrals

Authors: *D. KOTHAPALLI[1], M. A. TUBI[1], S. I. THOMOPOULOS[1], I. AGANJ[2], M. D. SWEENEY[3], X. WANG[4], L. S. SCHNEIDER[4,5], E. B. JOE[4], J. M. RINGMAN[4], H. N. YASSINE[6], M. G. HARRINGTON[7], B. V. ZLOKOVIC[3,8], A. W. TOGA[4,9], H. C. CHUI[4], P. M. THOMPSON[1,4,5], M. N. BRASKIE[1,4];
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Abstract: Regions of the medial temporal lobe (MTL) are integral to memory function[1]. Structural deficits in the entorhinal cortex[2] (ERC) and subiculum[3] may serve as early biomarkers for Alzheimer's disease (AD). Cortical thickness is a more sensitive measure of early AD-related changes than cortical volume[2]. Previous methods[4,5,6] to calculate thickness of these subregions can require tedious manual input. We propose an optimized pipeline that applies minimum line integrals[7] (MLI) to automatically calculate the thickness of MTL subregions using any

automated hippocampal subregion segmentation[8]. This method calculates thickness by finding the minimum distance between gray matter boundaries for all 3D lines drawn through a voxel. We aim to validate our method by evaluating if thinner ERC and subiculum values (calculated via MLI) are associated with *APOE*4 carrier status in non-demented subjects, consistent with previous findings.[2]

We used the ASHS[9] software[10] to segment T2-weighted hippocampal high-resolution MRI scans (0.4×0.4×2.0 mm) for 36 non-demented subjects from the USC ADRC cohort (Global CDR[11]= 0, mean age 67.5; 19 females; 17 *APOE*4+) using a study-specific atlas. We quality-checked the segmentation boundaries using an in-house protocol. We generated thickness maps by computing MLI[12] from binary masks for each subregion (left and right ERC and subiculum). We averaged thickness measures for all voxels at each point on the skeleton's surface to obtain a mean thickness value for each subregion. For each subregion, we used linear regression to study the association between mean thickness and *APOE*4 carrier status, adjusting for age, sex and years of education. We also evaluated the association between *APOE*4 carrier status and volumes of corresponding subregions as comparison, also adjusting for intracranial volume. The false discovery rate method (FDR) adjusted the expected proportion of false positives across 4 comparisons to <5%.

Lower mean cortical thickness (FDR-adjusted p=0.033, β=-0.419), but not volume (p=0.489), of the left subiculum alone was associated with *APOE4* genotype. Age was significantly associated with both cortical thickness and volume in all comparisons.

Our results are consistent with prior literature reporting that atrophy of the subiculum is the earliest hippocampal anatomical marker of AD[3]. Prior literature indicates asymmetric thinning of the left ERC in *APOE*4 carriers[13], similar to our findings in the left subiculum. Our results validate this automated method to calculate cortical thickness from a hippocampal subregion segmentation, facilitating research in AD and other disease cohorts where MTL subregions are implicated[14].

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Nanosymposium

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Title: Test re-test reliability of hippocampal subfield volume measures in developing sample: Implications for longitudinal developmental studies

Authors: *Q. YU, R. HOMAYOUNI, S. RAMESH, N. OFEN;
Inst. of Gerontology, Detroit, MI

Abstract: Human brain structure undergoes robust changes over development. Longitudinal structural magnetic resonance (MR) imaging studies are essential to map developmental trajectories of brain structures and understand how brain maturation supports cognitive development. In the field of episodic memory, current evidence suggests differential maturation patterns of hippocampal subfields underlie the observed unique developmental trajectories of distinct memory functions. However, the field lacks longitudinal data to test this intriguing hypothesis. Moreover, test re-test reliability in hippocampal subfield structure measures between sampling time points, the prerequisite of identifying meaningful developmental changes from longitudinal studies, is yet to be established. In current study, we examined test re-test agreement in hippocampal subfield structure measures in a developing sample (7-18 years, N = 13, M = 11.99, SD = 3.28) between two visits that are a month apart (mean delay = 32 days, SD = 4.49). We quantified hippocampal subfield structures on high-resolution T2-weighted MR images (0.4 × 0.4 × 2 mm^3) using a manual volumetry protocol with high inter-rater reliability (Intra-class correlation (2) ≥ 0.85), including regions of subiculum, Cornu ammonis (CA) sectors 1 and 2, combined CA3-dentate gyrus within the range of the hippocampal body. We found excellent agreement between hippocampal subfield volume measures of the two visits, assessed by two-way mixed intra-class correlation (ICC(2) single measures ≥ 0.95). We also used Bland-Altman plots to further assess the test re-test agreement. Volumetric differences between the two time points (volume at visit 1 - volume at visit 2) were not significantly different from zero ($|t| \leq 1.89$, $p \geq 0.08$), supporting agreement, except for left subiculum ($t = -2.99$, $p = 0.01$). Moreover, difference values were not related to mean values of the two visits, proxy for true volume measures, in any subfield (|Pearson's r| < 0.30, $p \geq 0.32$). This suggests no systematic disagreement between subfield volume measures from the two occasions exists that is proportional to true volume measures. Overall, our findings support excellent agreement between hippocampal subfield volume measures assessed by our manual demarcation protocol and MRI acquisition parameters.

Disclosures: Q. Yu: None. **R. Homayouni:** None. **S. Ramesh:** None. **N. Ofen:** None.

Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.08

Topic: I.03. Anatomical Methods

Support: Jacobs Foundation 20141151

Title: Hair cortisol concentrations are associated with hippocampal subregional volumes in early middle childhood

Authors: *Y. SHING[1,2], A. KERESZTES[2,3,4], L. RAFFINGTON[5], C. M. HEIM[6,7];
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Abstract: The human hippocampus, a brain structure crucial for learning and memory across the lifespan, is highly sensitive to adverse life events. In particular, childhood history of various extreme stress exposures has been linked to altered hippocampal structure and function in adults. Animal studies suggest that these differences are in part driven by aberrant glucocorticoid profiles during development, with the strongest effect on the dentate gyrus of the hippocampus. However, there is a paucity of human studies that examine these links, particularly in typically developing children exposed to a normative (i.e. non-traumatic) range of stress. In a sample of 84 children (age: 6-7 years), we assessed the associations between cumulative cortisol concentrations assessed from hair, volumes of distinct regions within the hippocampus, questionnaire-based parenting stress, and performance on memory tasks engaging the hippocampus. To delineate regions within the hippocampus, we implemented a pipeline previously described in Bender et al. (2018) using the Automated Segmentation of Hippocampal Subfields (ASHS) software tool (Yushkevich et al., 2015), with a custom atlas also created using ASHS from manual segmentations with excellent reliability from earlier studies in our laboratory. We found that higher concentrations of hair cortisol were specifically related to lower volumes of the CA3 and dentate gyrus (CA3-DG) region of the hippocampus. Interestingly, the CA3-DG-cortisol association did not manifest in effects on memory performance. These results suggest that the CA3-DG region of the hippocampus may be the most vulnerable hippocampal region to the adverse effects of stress hormones in early middle childhood. Currently ongoing analyses are examining the 2-year longitudinal changes of the subfield volumes in this sample, as well as to what extent individual differences in these longitudinal changes are related to memory development, cortisol, and stress measures.

Disclosures: A. Keresztes: None. **L. Raffington:** None. **C.M. Heim:** None. **Y. Shing:** None.

Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.09

Topic: I.03. Anatomical Methods

Support: HBP SGA2 Grant 785907

Title: Functional dynamics for successful recollection via pattern completion in medial temporal lobe and retrosplenial cortex

Authors: *X. GRANDE[1,2], D. BERRON[2,1,3], E. DUZEL[2,1,4];
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Abstract: Recollection requires successful pattern completion and cortical reinstatement of the encoded event representation. Theoretical work and sparse empirical evidence attribute both mechanisms to specific hippocampal subfields, i.e. CA3 and CA1 respectively. In addition, involvement of the retrosplenial cortex has been suggested to assure a vivid recollective experience of the encoded scenery. Here, we employed an extensively piloted novel scene - object retrieval paradigm to directly investigate the functional dynamics within and between retrosplenial cortex and the medial temporal lobe, specifically the hippocampus that are required for successful pattern completion and recollection. Participants encoded scenes (rooms) containing two objects and subsequently recalled the objects based on empty scene cues. High-resolution functional data in younger adults (YA) has been obtained as well as whole-brain functional data in a cohort of older adults with assessed amyloid status and subjective cognitive impairment (OA), a potential risk state for Alzheimer's dementia (AD). Univariate results show reactivation of cortical regions associated with object processing when objects are recalled upon empty scene cues. The high-resolution data allows to directly test the hypothesis that this reinstatement is driven by hippocampal subfields CA1 and CA3/DG. We will apply multivariate analyses to reveal the underlying cue completion process in the medial temporal lobe on representational level, the level of its theoretical definition. Crucially, we hypothesize the preciseness of the recollective experience to depend on associated retrosplenial dynamics. We will also examine the functional underpinnings of reported pattern completion impairment in OA, and for the first time, we will be able to test the hypothesis that hypoactivity in the retrosplenial cortex, previously associated with presymptomatic amyloid pathology, affects the recollective experience. The unique combination of a novel pattern completion paradigm, high-resolution functional data in YA and whole-brain functional data in an AD-risk cohort contributes to our empirical understanding of recollection via pattern completion and sheds light on the functional alterations elicited by early AD pathology.

Disclosures: X. Grande: None. **D. Berron:** None. **E. Duzel:** None.

Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.10

Topic: I.03. Anatomical Methods

Support: Weston Brain Institute

Title: Comparing the impact of T1- and T2-weighted acquisition on automated hippocampal subfield volume estimates

Authors: *A. BUSSY[1,4], E. PLITMAN[2,4], S. A. BEDFORD[1,4], A. SALACIAK[4], S. FARZIN[4], S. TULLO[1,4], M.-L. BELAND[4], G. A. DEVENYI[4,2], M. CHAKRAVARTY[4,1,2,3];
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Abstract: *Introduction*: The hippocampus and its subfields play an important role in memory function. Here we compare the impact of magnetic resonance image (MRI)-acquisition on automatically derived estimates of hippocampal subfield volumes and subsequent analyses of ageing trajectories across the adult lifespan.
Methods: We used the MAGeT Brain algorithm to estimate the volumes of hippocampal subfields and associated white matter regions (Cornus Ammonis [CA]1, CA2CA3, CA4 and dentate gyrus (CA4DG), stratum radiatum/lacunosum/moleculare, subiculum, fimbria, fornix, alveus, and mammillary bodies) in 147 healthy adults (18-80 years old) using both standard T1-weighted (T1w; 1mm3 voxels) and high-resolution T2-weighted (T2w; 0.64mm3 voxels) images acquired on a 3T Siemens Trio. The mean percentage volume difference, Pearson correlation coefficients (PCCs), and Dice similarity coefficients (DSC) of the volumes were used to compare estimates. The associations between volumes and age were investigated using general linear models (including sex, years of education, APOE4 status, ipsilateral hippocampal grey matter or white matter volume as covariates; all comparisons surviving $p<0.05$ Bonferroni corrected reported).
Results: Subfield volumes from standard T1w images show similarity with estimates from T2w images (PCC range: 0.84-0.96; DSC range: 0.88-0.97). T2w volumes underestimated (up to 19%) the volumes of certain subfields (e.g. CA2CA3, subiculum, alveus, fimbria, fornix, and mammillary bodies), and overestimate the volumes in others (e.g. CA1 and CA4DG; up to 6.1%) relative to T1w-derived volumes. A positive relationship was found with age for the right and left CA1 and the right alveus in both the T1w and T2w analyses. T1w analyses showed that the right CA4DG was negatively related to age and the left alveus was positively related to age. Furthermore, the left CA2CA3 and the right fornix were found to be negatively related to age in T2w analyses.
Conclusion: The current work suggests although T1w and T2w derived subfield volumetric outputs are similar, modality choice will play a significant role in the nature of their relationship

to biological findings. Further investigation is required into the trade-offs that may occur based on this design choice.

Disclosures: **A. Bussy:** None. **E. Plitman:** None. **S.A. Bedford:** None. **A. Salaciak:** None. **S. Farzin:** None. **S. Tullo:** None. **M. Beland:** None. **G.A. Devenyi:** F. Consulting Fees (e.g., advisory boards); MIAC AG. **M. Chakravarty:** None.

Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.11

Topic: I.03. Anatomical Methods

Support: NIH HD079518

Title: Longitudinal examination of associations between young children's pattern separation abilities and hippocampal subfield volumes

Authors: *T. RIGGINS, K. L. CANADA;
Univ. of Maryland, College Park, MD

Abstract: Subfields of the hippocampus display protracted developmental trajectories. Cross-sectional research in children has suggested that developmental differences in volume of hippocampal subfields is associated with age-related differences in performance on tasks that are thought to rely on these structures. For example, relations between volume of dentate gyrus/CA2-4 (DG/CA2-4) has been related to children's performance on a modified Mnemonic Similarity Test (MST), which reflects pattern separation (Canada et al., 2018). In this study, indices of pattern separation abilities tracked normative patterns of increases and decreases in volume over this age range. That is, greater volume was related to better performance in younger children, whereas in older children, smaller volume was related to better performance. However, whether these age-related differences reflect age-related change within an individual remains unknown. In this study, we used an accelerated longitudinal design to examine relations between hippocampal subfield volumes and pattern separation as indexed by bias-corrected measures of lure discrimination on a MST in a sample of 113 children (4-8 years). Bilateral subiculum, CA1, and DG/CA2-4 volumes were derived for head and body of the hippocampus from ultra-high resolution T2-weighted structural MRI scans. Manual tracing was conducted on 20 cases using boundaries described by La Joie et al. (2010) and used in conjunction with the Automatic Segmentation of Hippocampal Subfields software (Yushkevich et al., 2014) to yield volumes for all participants. Volumes were corrected for intracranial volume. Preliminary results indicate an interaction between age and DG/CA2-4 body volume when predicting pattern separation indices. Specifically, volume was positively correlated with pattern separation ability in younger (4-6

years) but not older children (7-8 years). These findings replicate cross-sectional work in a longitudinal sample, and extend them by showing this effect is driven by subfields in the body as opposed to head of the hippocampus. In addition, these findings support the proposal that developmental changes in hippocampal circuitry are crucial for the maturation of the formation of memories with high-resolution details during early childhood.

Disclosures: T. Riggins: None. **K.L. Canada:** None.

Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.12

Topic: I.03. Anatomical Methods

Support: NIH Grant R00 AG036818
NIH Grant R00 AG036848
NIH Grant R01 AG056535

Title: The role of hippocampal subfield volume and fornix microstructure in episodic memory across the lifespan

Authors: *C. M. FOSTER, K. M. KENNEDY, D. A. HOAGEY, K. M. RODRIGUE;
Ctr. For Vital Longevity | UT Dallas, Dallas, TX

Abstract: Advancing age is associated both with declines in episodic memory, with an emphasis on associative as compared to item memory, and degradation of medial temporal lobe (MTL) structures. Previous research has established the critical role of MTL in supporting episodic memory; however, the contribution is complex and depends upon the interplay among hippocampal subfields and surrounding parahippocampal and entorhinal cortices and fornix. Despite the established role of MTL in supporting episodic memory, the differential contributions of MTL system components in mediating age effects on memory remain unclear. The current study uses structural equation modeling to test whether the relationship between age and associative memory, as compared to item memory, is mediated by MTL structure, as well as the degree to which MTL circuitry may inform this mediation. In a sample of 177 healthy individuals aged 20-94 we collected high-resolution T1-weighted, ultra high-resolution T2/PD, and diffusion-weighted MRI sequences on a 3T Phillips Achieva scanner. Hippocampal subfield and entorhinal cortex volumes were measured from T2/PD weighted scans using a combination of manual tracings and the Automated Segmentation of Hippocampal Subfields pipeline (Yushkevich et al., 2014). Parahippocampal gyrus volume was estimated using Freesurfer and DTI scans were used to obtain diffusion metrics from deterministic tractography of the fornix. Associative and item memory constructs were formed from multiple standardized tests. To

investigate whether and how MTL structure mediated age effects on associative and/or item memory, we specified four competing structural equation models estimating MTL circuitry based pathways. The most parsimonious, best-fitting model included pathways through a latent construct of hippocampal input (i.e., the parahippocampal gyrus and entorhinal cortex), hippocampus proper (i.e., a single hippocampal construct which combined all subfields), and hippocampal output (i.e., fornix diffusion measured using fractional anisotropy and mean diffusivity). Results indicated that 1) fornix microstructure independently mediated the effect of age on associative memory; 2) all regions and estimated paths (including fornix) combined to significantly mediate the age-associative memory relationship. None of the regions mediated item memory-age association. These findings suggest that preservation of fornix connectivity and medial temporal lobe structure with aging is important for maintenance of associative memory performance across the lifespan.

Disclosures: C.M. Foster: None. **K.M. Kennedy:** None. **D.A. Hoagey:** None. **K.M. Rodrigue:** None.

Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.13

Topic: I.03. Anatomical Methods

Support: EU Joint Programme - Neurodegenerative Disease Research

Title: Hippocampal subfields group progress update: Harmonization of a protocol for segmenting human hippocampal subfields on MRI

Authors: *V. A. CARR[1], D. BERRON[2], A. M. DAUGHERTY[3], R. K. OLSEN[5], L. WISSE[6], K. M. AMUNTS[9], J. C. AUGUSTINACK[10], A. BAKKER[11], A. R. BENDER[12], M. BOCCARDI[13], M. BOCCHETTA[14], M. CHAKRAVARTY[15], G. CHETELAT[16], R. DE FLORES[7], J. DEKRAKER[17], S.-L. DING[18], R. INSAUSTI[19], O. KEDO[20], S. MUELLER[21], N. OFEN[4], D. J. PALOMBO[23], N. RAZ[4], C. E. STARK[24], L. WANG[25], P. YUSHKEVICH[8], Q. YU[26], R. LA JOIE[22];
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Canada; [16]Inserm EPHE UCBN U1077, Caen, France; [17]Neurosci., Western University, Brain and Mind Inst., London, ON, Canada; [18]Allen Inst. For Brain Sci., Seattle, WA; [19]Sch. of Medicine, HNL, Univ. of Castilla-La Mancha - Q13680009E, Albacete, Spain; [20]Inst. of Neurosci. and Med., Res. Ctr. Jülich, Jülich, Germany; [21]Radiology, [22]Neurol., Univ. of California San Francisco, San Francisco, CA; [23]Psychology, Univ. of British Columbia, Vancouver, BC, Canada; [24]Univ. of California Irvine, Irvine, CA; [25]Psychiatry, Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [26]Inst. of Gerontology, Detroit, MI

Abstract: The number of studies using high-resolution MRI to examine the structure and function of human hippocampal subfields has soared in recent years. However, substantial differences in subfield definitions across groups has hindered the ability to compare results and draw conclusions across studies. The Hippocampal Subfields Group (HSG) has been working to remedy this problem by creating a valid and reliable harmonized segmentation protocol for high-resolution T2-weighted 3T MRI (http://www.hippocampalsubfields.com). Given substantial differences in the anatomy of the hippocampal head, body, and tail, we have approached these regions separately using the following workflow: 1) collect histology samples labeled by expert neuroanatomists to guide development of the MRI segmentation protocol, 2) develop hippocampal subfield boundary definitions, 3) assess HSG community agreement with these definitions via online questionnaires and revise as needed, and 4) test reliability of boundary definitions on multiple MRI data sets. For both the hippocampal body and head, we have developed a preliminary segmentation protocol by completing steps 1 and 2, and we are in the process of developing a protocol for the hippocampal tail. We have also completed the community assessment/boundary revision process (step 3) for the outer boundaries of the hippocampal body. With respect to inner boundaries (e.g., between the cornu ammonis fields), the assessment/revision process is underway. Step 4, reliability testing of the protocol, is underway for the outer boundaries of the hippocampal body, and we will proceed with other portions of the hippocampus once the assessment/revision process is complete. Once finalized, the harmonized protocol will significantly facilitate cross-study comparisons, thus advancing our understanding of the structure and function of hippocampal subfields across the lifespan in both health and disease.

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Nanosymposium

456. Human Brain Mapping and Imaging in Health and Diseases

Location: Room S402

Time: Tuesday, October 22, 2019, 8:00 AM - 11:30 AM

Presentation Number: 456.14

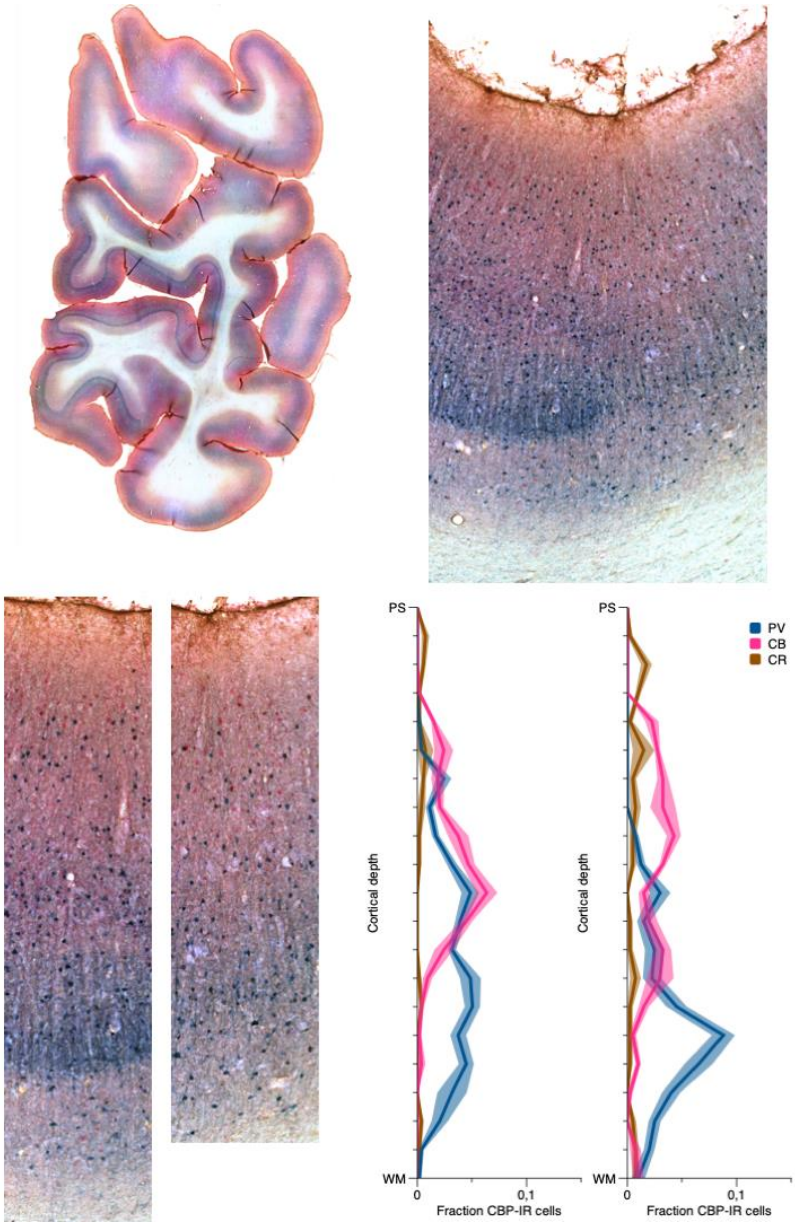
Topic: I.03. Anatomical Methods

Support: Human Brain Project SGA2 785907

Title: Quantitative mapping of calcium binding protein expressing inhibitory interneurons in human visual cortex

Authors: R. N. KOOIJMANS[1,2], E. UPSCHULTE[2], T. DICKSCHEID[2], K. ZILLES[2], K. M. AMUNTS[2], *P. R. ROELFSEMA[1];
[1]Vision & Cognition, Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Inst. of Neurosci. and Med., Res. Ctr. Jülich, Jülich, Germany

Abstract: Mouse models have led the establishment of new molecular markers and have engendered a rise in understanding cell-specific function. Information based on such markers in the human brain is highly fragmented, and major parts are missing. While cell types often exhibit homology across species, the size and organizational complexity of the human brain make direct inference of function from mouse data problematic. Furthermore, antibody-based staining in human tissue is typically less reliable than in mouse brain tissue, and the large size of full-hemisphere human brain section immunohistochemistry is methodically challenging. As a result, the combination of several antibodies in one and the same large-scale section is particularly novel.We have developed a new procedure that allows us to label, visualize, segment, classify, and quantify distinct cell populations, as defined by protein expression (figure). We perform triple immunohistochemistry for calcium binding proteins parvalbumin, calbindin and calretinin in full-hemisphere sections of the human brain, and image them at 1µm resolution, using fast, full-colour, bright-field scanning. Subsequently, we segment the stained cell bodies using machine learning, and separate the different populations based on color, to describe cellular distributions with high accuracy. Based on this method, we are able to generate novel high-resolution maps of protein distribution in human visual cortex.We show that we can specifically, reliably, and quantitatively map subsets of cells based on their protein expression with respect to cortical layers, and deliver information about human brain architecture which is highly complementary to existing data. Acquired data will be integrated into the multilevel atlas of the Human Brain Project as maps for specific cell types linked to cytoarchitectonic maps in the microscopic resolution Big Brain model. Through this atlas, the data is available to the broader research community.



Disclosures: **R.N. Kooijmans:** None. **E. Upschulte:** None. **T. Dickscheid:** None. **K. Zilles:** None. **K.M. Amunts:** None. **P.R. Roelfsema:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.01

Topic: A.07. Developmental Disorders

Title: Dissecting the molecular basis of MTOR somatic mutations in aberrant brain development and neural circuit formation

Authors: *S. PARK[1], J. LIM[1], S. RAMAKRISHINA[2], S. KIM[3], W. KIM[1], J. LEE[4], H.-C. KANG[3], J. F. REITER[5], D. KIM[3], H. KIM[3], J. LEE[1];
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Abstract: Focal malformations of cortical development (FMCDs), including focal cortical dysplasia (FCD) and hemimegalencephaly (HME), are major etiologies of pediatric intractable epilepsies exhibiting cortical dyslamination. Brain somatic mutations in *MTOR* have recently been identified as a major genetic cause of FMCDs. However, the molecular basis of *MTOR* somatic mutations in aberrant brain development and neural circuit formation remains poorly understood. Especially, the molecular mechanism by which these mutations lead to cortical dyslamination is still elusive. Here, using patient tissue, genome-edited cells, and mouse models with brain somatic mutations in *MTOR*, we discovered that disruption of neuronal ciliogenesis by the mutations underlies cortical dyslamination in FMCDs. We found that abnormal accumulation of OFD1 at centriolar satellites due to perturbed autophagy was responsible for the defective neuronal ciliogenesis. Additionally, we found that disrupted neuronal ciliogenesis accounted for cortical dyslamination in FMCDs by compromising Wnt signals essential for neuronal polarization. Next, we are trying to dissect the molecular basis of *MTOR* somatic mutations in aberrant neural circuit formation causing epileptic neural network, with several techniques including virus injection for neuronal tracing, optogenetics, and single-unit recording. We observed aberrant neuronal projection and firing, both of which are attributable to *MTOR* somatic mutations. We plan to modulate the defective neural circuits with optogenetics for dissecting the causal role of these circuits on aberrant behavioral phenotypes seen in FMCDs, such as epilepsy and anxiety. Altogether, this study describes a molecular basis by which brain somatic mutations in *MTOR* contribute to the pathogenesis of FMCDs.

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Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.02

Topic: A.07. Developmental Disorders

Title: Sex differences in microRNA expression in human 2nd trimester fetal brain

Authors: *C. C. TOSTE, M. C. O'DONOVAN, M. J. HILL, N. J. BRAY;
MRC Ctr. for Neuropsychiatric Genet. & Genomics, Cardiff Univ., Cardiff, United Kingdom

Abstract: MicroRNAs (miRNAs) are a class of small (18-25 nucleotide) non-coding RNAs that regulate gene expression by targeting specific mRNAs for degradation or translational repression. MiRNAs are highly expressed in the brain where they regulate processes affecting brain development and neuronal function. Altered miRNA expression has been reported in post-mortem brains of individuals with various neuropsychiatric disorders, including neurodevelopmental disorders such as autism spectrum disorder (ASD) and intellectual disability, which differ substantially in both prevalence and presentation between sexes. Given the importance of miRNAs in brain development, identifying sex biased miRNA expression may be highly informative for understanding both brain sex differences and mechanisms underpinning psychiatric disorders. Small RNA sequencing was performed on 60 human brain samples from the second trimester of gestation (12-20 post conception weeks). Reads were aligned to both miRbase (v.21) and reference genome (GRCh38, v24) using STAR aligner. Aligned reads were quantified into raw counts using featureCounts and normalized by TMM. Fetal sex had been previously determined by karyotyping, expression of genes on the Y-chromosome in males and heterozygosity for genetic X-chromosome markers in females. Differential expression analyses between males and females were performed using EdgeR, controlling for the false discovery rate (FDR) at 0.05. A total of seven mature microRNAs were differentially expressed between male and female prenatal brain ([FDR] < 0.05), and were located exclusively in autosomes. Of these, two miRNAs exhibited higher expression in males (miR-181a-5p and miR-10395-5p) and five miRNAs were more highly expressed in females (miR-373-3p, miR-202-5p, miR202-3p, miR-372-3p and miR-302a-5p). Interestingly, miR-181a-5p has been shown to target oestrogen receptor ERα. This study begins to disentangle sex differences in microRNA expression in the fetal brain, which could contribute to sexual dimorphism in brain function and risk for neurodevelopmental disorders.

Disclosures: C.C. Toste: None. **M.C. O'Donovan:** None. **M.J. Hill:** None. **N.J. Bray:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.03

Topic: A.07. Developmental Disorders

Support: Philanthropic donations to the Center for Rare Childhood Disorders at TGen

Title: Two males with X-linked, syndromic mental retardation carry *de novo* mutations in HNRNPH2

Authors: *W. M. JEPSEN[1,2,3], K. RAMSEY[2], S. SZELINGER[2], L. LLACI[1,2], C. BALAK[1,2], N. BELNAP[2], C. BILAGODY[1,2], M. DE BOTH[1,2], R. GUPTA[1], M. NAYMIK[1,2], R. PANDEY[1,2], I. S. PIRAS[1,2], M. SANCHEZ-CASTILLO[2], S. RANGASAMY[1,2], V. NARAYANAN[1,2], M. J. HUENTELMAN[1,2,3];
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Abstract: We have identified two males carrying *de novo* missense mutations in the HNRNPH2 gene, one of which was previously identified in females with mental retardation, x-linked, syndromic, Bain-type by Bain et al., and presumed to be embryonically lethal in males. Patient A is hemizygous for a MRXSB mutation originally identified in 3 females within the nuclear localization sequence of *HNRNPH2* (c.616C>T, p.Arg206Trp), serving as conclusive evidence that known MRXSB mutations are not embryonically lethal in males. Patient B is hemizygous for a private mutation in the second RNA recognition motif (RRM2) of *HNRNPH2* (c.340C>T, p.Arg114Trp), suggesting that other mutations within this gene are capable of producing a range of similar phenotypes.
Patient A is a 5-year-old male. Whole exome sequencing (WES) was performed on the patient and biological parents revealing a *de novo*, missense mutation, HNRNPH2(R206W), that has been previously associated with MRXSB. The variant was confirmed by Sanger sequencing. Phenotypic overlaps with heterozygous females include developmental delay with regression, tone abnormalities, brain abnormalities, and growth problems. Restriction fragment length polymorphism and Sanger sequencing of genomic DNA from the patient's fibroblasts reveals low-level mosaicism for the reference allele.
Patient B is an 8-year-old male with global developmental delay, microcephaly, failure to thrive, intractable epilepsy, hypotonia, and cortical visual impairment. WES identified a private, *de novo*, missense mutation in *HNRNPH2* (c.340C>T, p.Arg114Trp) that was confirmed by Sanger sequencing. The variant has a CADD PHRED of 22.4 and is considered likely pathogenic by the American College of Medical Genetics (ACMG) classification (rules: PS2, PM2). The mutation is predicted to affect protein function by SIFT (sift.bii.a-star.edu.sg) with a score of 0.00 (median sequence conservation=3.07, sequences represented=29), and MutationTaster (mutationtaster.org) predicts it is disease causing (accuracy=0.9999, converted rank score=0.5881). WES revealed 5 reference reads (7%) and 64 variant reads (93%) at the position, implying low level mosaicism for the reference allele. Phenotypic overlaps with MRXSB include developmental delay, seizures, tone abnormalities, and growth problems.
Our data demonstrate that known MRXSB mutations in *HNRNPH2* are not embryonically lethal in males, which may be due to low-level mosaicism of the reference allele, and we add to the literature that other deleterious mutations within the gene are likely capable of producing a range of overlapping phenotypes.

Disclosures: W.M. Jepsen: None. **K. Ramsey:** None. **S. Szelinger:** None. **L. Llaci:** None. **C. Balak:** None. **N. Belnap:** None. **C. Bilagody:** None. **M. De Both:** None. **R. Gupta:** None. **M. Naymik:** None. **R. Pandey:** None. **I.S. Piras:** None. **M. Sanchez-Castillo:** None. **S. Rangasamy:** None. **V. Narayanan:** None. **M.J. Huentelman:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.04

Topic: A.07. Developmental Disorders

Support: HBHL
CIHR
FRQS

Title: Early and late prenatal maternal inflammation alters fetal and neonatal brain volume

Authors: *E. GUMA[1,4], E. SNOOK[6,5], G. DESROSIERS-GREGOIRE[1], G. A. DEVENYI[4], S. SPRING[8], J. P. LERCH[8,7,9], M. CHAKRAVARTY[4,2,3];
[1]Integrated Program in Neurosci., [2]Dept. of Psychiatry, [3]Dept. of Biol. and Biomed. Engin., McGill Univ., Montreal, QC, Canada; [4]Cerebral Imaging Ctr., [5]Douglas Univ. Mental Hlth. Institute, McGill, Montreal, QC, Canada; [6]Dept. of Med., [7]Dept. of Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [8]The Hosp. For Sick Children, Toronto, ON, Canada; [9]Wellcome Ctr. for Integrative Neuroimaging, Univ. of Oxford, Oxford, United Kingdom

Abstract: Maternal immune activation (MIA) in pregnancy elevates risk for neurodevelopmental disorders in offspring. It is unknown if abnormalities are dependent on MIA-timing or detectable in fetal/neonatal periods. This work investigates effects of MIA-timing on embryonic and neonatal brain structure and neonatal communicative behaviour.
Pregnant dams (C57BL6) were injected with poly I:C (POL; 5mg/kg ip) or vehicle (SAL) at gestational day (GD) 9(E) or 17(L). Embryos (GD18) were extracted and fixed using 4% PFA and 2% Gadolinium (MRI contrast agent). Neonate (P8) ultrasonic vocalizations (USV) were recorded (n=14-25/sex/group) followed by sacrifice and fixation via intracardiac perfusion. Ex vivo T2-weighted structural MRIs (40μm3; 7T Varian) were collected at MICe, Toronto (n sex/group: embryo n=8-15; neonate n=13-19). Deformation-based morphometry was used to calculate voxel-level brain volume differences, examined with a linear mixed effects model for sex by group interactions (litter size as random intercept; False Discovery Rate [FDR] corrected). USVs were assessed for group and variance differences using a linear model and Fligner-Killeen Test, respectively.
The sex by group interaction was not significant for embryos or neonates. POL E embryos had larger isocortex, basal ganglia, septum and hippocampus than SAL E (<15%FDR; Fig1B). POL L embryos had brain-wide volume increases compared to SAL L (<1%FDR; Fig1C). POL E neonates had larger motor and somatosensory cortices, hippocampus, and smaller thalamic and cerebellar nuclei than SAL (<1% FDR; Fig1D). POL L neonates had larger somatosensory and motor cortices, and smaller thalamic nuclei (<5% FDR; Fig1E). No differences in USV mean call duration were observed, however POL E and L offspring had significantly greater variance than SAL (X2=93.15,p=0.00001), particularly in males (X2=3.95, p= 0.047) (Fig1F).

We show striking fetal and neonatal brain alterations following MIA. A better understanding of these alterations can elucidate mechanisms underlying neurodevelopmental disorders.

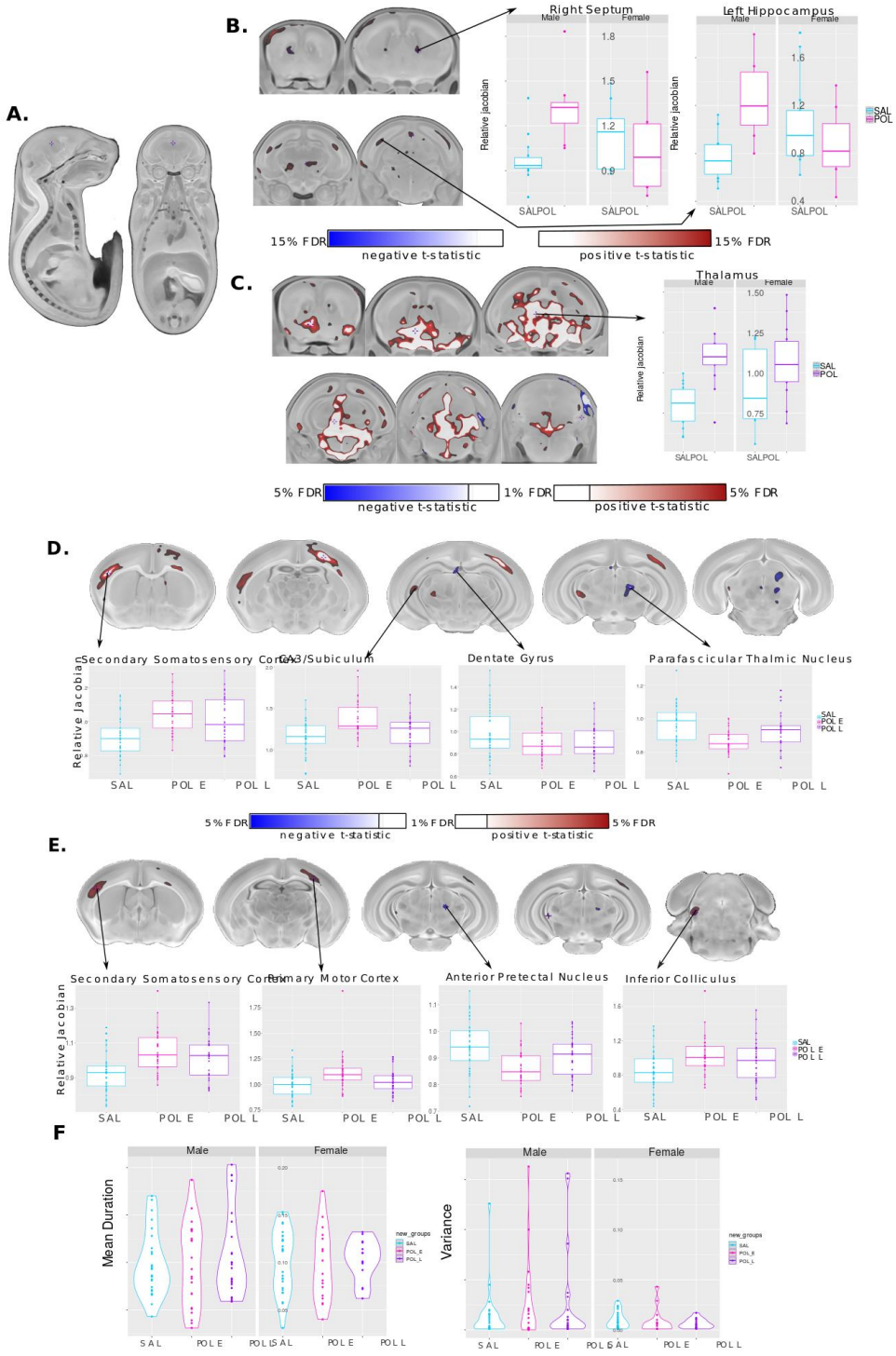

Figure 1. Pre- and postnatal neurodevelopmental alterations following maternal immune activatic **A**. Representative image of whole embryo scan. Local brain volume changes between the POL SAL E embryos (**B**), and POL L and SAL L embryos (**C**). Local brain volume changes between t E and SAL neonates (**D**), and POL L and SAL neonates (**E**). No differences in mean, but differer variance of USV call duration in early and POL L exposed neonates compared to SAL (**F**).

Disclosures: **E. Guma:** None. **E. Snook:** None. **G. Desrosiers-Gregoire:** None. **G.A. Devenyi:** None. **S. Spring:** None. **J.P. Lerch:** None. **M. Chakravarty:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

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Presentation Number: 535.05

Topic: A.07. Developmental Disorders

Support: HIAS15004 2014-2018 Hussman Foundation Pilot Grant
MSCRFD-3815 2017-2019 Maryland Stem Cell Research Fund Discovery Grant

Title: Human induced pluripotent stem cell-derived 3D organoids combined with high-content screening reveal network-level phenotypes in a subset of individuals with idiopathic autism

Authors: ***M. DURENS**[1], J. NESTOR[1], K. HEROLD[1,2], M. W. NESTOR[1,2];
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Abstract: The cellular phenotyping of neurons from individuals with Autism Spectrum Condition (ASC) has proven to be a major challenge for the field. One of the hypothesized models for the pathogenesis of ASC suggests that dysregulation of the balance between excitatory and inhibitory (E/I) neuronal inputs may underly some phenotypic aspects of ASC. A precise E/I ratio is required to maintain the narrow range of optimal neuronal spiking required for the transfer of information within the brain. Neurodevelopmental deficits in γ-aminobutyric acid (GABA)ergic or glutamatergic neurons may contribute to an imbalance in this E/I ratio. By using human induced pluripotent stem cell (hiPSC)-derived neurons in a 3D model system we can investigate these potential deficits in an *in vitro* model system that may more accurately recapitulate human cortical development. The objective of this study was to use a 3D serum free embryoid body (SFEB) organoid model to assess for potential differences in the morphology and network-level function that are specific to cortical neurons derived from ASC patient hiPSCs. High throughput approaches were applied to compensate for heterogeneity and variability inherent in 3D cultures. To model ASC neuronal phenotypes in our cohort of patients, SFEBs were generated from control and ASC individuals (n = 4 lines and 7 lines, respectively). High content screening using the ThermoFisher ArrayScan XTi platform was used to quantify $GABA^+$ and $VGLUT^+$ cells in SFEBs and $VGLUT^+$ neuron morphology. Spontaneous network-level activity was recorded from SFEBs plated onto multi-electrode array (MEA) plates. High content analysis revealed that SFEBs derived from individuals with ASC have fewer $GABA^+$ neurons as compared to controls (N = 288 SFEBs/line, $p<0.001$; Mann-Whitney U). However, there was no difference in the number of $VGLUT^+$ neurons in individuals with ASC compared to controls using the same analysis. A high content screen of the morphology of $VGLUT^+$ neurons showed a

decrease in the number of branch points and number of neurites in ASC lines compared to controls (N = 288 SFEBs/line, $p<0.001$; Mann-Whitney U). MEA recordings reveal that SFEBs derived from individuals with ASC show increased spontaneous firing (N = 72 SFEBs/line, $p<0.001$; Mann-Whitney U). Whether this increase is influenced by reduced number of $GABA^+$ neurons and decreased inhibition ASC-derived SFEBs warrants further investigation by evaluating the dynamics of $GABA^+$ and $VGLUT^+$ populations surrounding active MEA electrodes. These findings indicate that potential E/I deficits found in our ASC cohort can be detected using high-content approaches.

Disclosures: **M. Durens:** None. **J. Nestor:** None. **K. Herold:** None. **M.W. Nestor:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

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Presentation Number: 535.06

Topic: A.07. Developmental Disorders

Support: R01NS099405
T32 GM07215

Title: Human axon guidance is aberrant in an iPS model of tuberous sclerosis complex via a RhoA-dependent pathway

Authors: *T. S. CATLETT[1,2], M. M. ONESTO[1], A. J. MCCANN[3], S. K. REMPEL[1,2], T. M. GOMEZ[1];
[1]Dept of Neurosci., [2]Cell. and Mol. Biol., [3]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Animal models have served to answer many questions of axon guidance mechanisms *in vitro* and *in vivo*, and to provoke speculation as to their conservation in human development. Now, human induced pluripotent stem cell (iPS)-derived neurons allow us to further our understanding of axon guidance during normal human development and within a neurodevelopmental disease context. As of yet, however, no studies have illuminated this crucial area. We utilize iPS and ES lines to differentiate human forebrain and motor neurons and show these cells respond to canonical guidance cues via growth promotion, inhibition, and guidance. Moreover, utilizing an iPS disease model of Tuberous Sclerosis Complex (TSC) with a mutation in TSC2, a key negative regulator of protein synthesis within growth cones, we show a role for TSC2-dependent cytoskeletal modulation of RhoA downstream of guidance cues. Our results suggest that neural network connectivity defects in patients with TSC, an autism spectrum disorder, may result from defects in direct RhoA regulation of the cytoskeleton. Contra some animal model systems, local protein synthesis was not required for a collapse response to canonical guidance cues in human growth cones. Our work shows *in vitro* axon guidance in a

human model system and axon guidance deficits in an iPS-derived human disease model, and furthermore demonstrates that in some respects human neurodevelopmental mechanisms may diverge from animal models, and thus we hope this study will promote further investigation into these questions.

Disclosures: **T.S. Catlett:** None. **M.M. Onesto:** None. **A.J. McCann:** None. **S.K. Rempel:** None. **T.M. Gomez:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

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Presentation Number: 535.07

Topic: A.07. Developmental Disorders

Support: AG057408
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NS094154
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T32 GM007507
P41 GM108538

Title: Dysregulated acetyl-CoA homeostasis causes metabolic and synaptic abnormalities in neurodevelopment

Authors: *I. A. DIETERICH[1,2], N. H. ROBINSON[1,2], K. A. OVERMYER[3], A. PETERSEN[2], J. J. COON[3], S.-C. ZHANG[2], A. BHATTACHARYYA[2], L. PUGLIELLI[1,2];
[1]Med., [2]Waisman Ctr., [3]Chem. and Biomolecular Chem., Univ. of Wisconsin Madison, Madison, WI

Abstract: Nε-lysine acetylation of nascent folded polypeptides regulates proteostasis within the Endoplasmic Reticulum (ER). In order for acetylation to occur, cytosolic acetyl-CoA must be imported into the ER by the ER-membrane transporter, *AT-1/SLC33A1*. Gene duplications in *AT-1* have been identified in patients with autistic-like features, intellectual disability, and dysmorphic features. Importantly, we have shown that the levels of cytosolic Acetyl-CoA influence the secretory pathway, autophagy, mitochondria energetics, and lipid metabolism in the cytosol. We have identified three genes which maintain this crosstalk - *Slc25a1*, *Acly*, and *Slc13a5* - and display a unique compensatory mechanism to maintain homeostasis of cytosolic acetyl-CoA. ***Slc25a1*** is the mitochondria membrane transporter that translocates citrate from the mitochondria to the cytosol; ATP citrate lyase, ***Acly,*** is a cytosolic-based enzyme that converts citrate into acetyl-CoA using cytosolic CoA and ATP; ***Slc13a5*** is a plasma membrane citrate

transporter that translocates citrate from the *extracellular milieu* to the cytosol. Interestingly, gene duplication events of *Slc25a1*, *Acly*, *Slc13a5*, and *AT-1/SLC33A1* have all been associated with Autism Spectrum Disorder (ASD) and progeria-like features.
Here, we have investigated the synaptic and metabolic consequences of dysregulated acetyl-CoA flux by generating human pluripotent stem cell lines overexpressing *Slc25a1*, *Acly*, and *Slc13a5*. *Slc25a1, Acly*, and *Slc13a5* are key regulatory entry points for cytosolic acetyl-CoA metabolism. Indeed, we discovered a compensatory mechanism in place to maintain these acetyl-CoA levels: specifically, overexpression of one target protein causes an upregulation of the other (endogenous) crosstalk proteins. We next examined mitochondria adaptation using ^{13}C labeled flux analysis of TCA pathway engagement. Interestingly, *Slc13a5* and *Slc25a1* show a marked increase of the TCA intermediates, whereas *Acly* shows a marked decrease in TCA intermediates and an increase in short and long chain carnitines. Human neurons differentiated from these stem cells revealed dramatic phenotypes. Overexpression of *Slc13a5* resulted in a cytotoxic response. *Slc25a1* and *Acly* overexpression show synaptic abnormalities - both at a morphological and synaptic activity level. These data demonstrate that acetyl-CoA homeostasis, as regulated by *Slc25a1, Acly, Slc13a5*, and *AT-1/SLC33A1*, impinges on metabolic and synaptic function, and that dysregulated acetyl-CoA flux plays an important neurobiological role in ASD.

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Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.08

Topic: A.07. Developmental Disorders

Support: NIH 1F31MH118883-01

Title: Oxidative stress and mitochondrial dysfunction in parvalbumin interneurons following perinatal NMDAR blockade in mice

Authors: *A. J. PHENSY[1], D. BAIRUTY[3], E. GAUBA[4], K. A. LINDQUIST[5], K. LINDQUIST[1], L. GUO[2], N. SRINIVASAN[1], S. GANDHI[1], H. DU[2], S. KROENER[1]; [1]Behavioral and Brain Sci., [2]Biol. Sci., Univ. of Texas at Dallas, Richardson, TX; [3]TCOM, Fort Worth, TX; [4]Stanford, Stanford, CA; [5]UT Southwestern, Dallas, TX

Abstract: Schizophrenia is thought to arise from neurodevelopmental disturbances that reflect the interaction between genetic susceptibility and environmental risk factors. Redox dysregulation and oxidative stress may be a final common pathway in the pathophysiology of the

disease, causing dysfunction of GABAergic interneurons, which are crucial for the coordination of neuronal synchrony during sensory and cognitive processing. Mitochondria are a major source of reactive oxygen species (ROS) in neurons, and they are both a pivotal contributor and amplifier of intracellular oxidative stress in pathological states. The mitochondrial matrix protein cyclophilin D (CypD) modulates the mitochondrial permeability transition (MPT), which causes release of mitochondrial ROS, initiating a feed-forward cycle of ROS generation and release, metabolic changes, and eventual loss of cell function. Here, we show that CypD is upregulated in GABAergic parvalbumin interneurons (PVI) in prefrontal cortex (PFC) tissue obtained from schizophrenia patients. In addition, we show that CypD-mediated MPT is directly involved in loss of PVI function in an animal model of NMDA-hypofunction. Perinatal blockade of NMDA receptors induces persistent behavioral deficits in cognition, memory, and social behavior in adult mice. These changes correlate with reduced PVI immunoreactivity and increased levels of mitochondrial-derived ROS in PVI of the PFC. However, genetic deletion of CypD (via ablation of the Ppif gene) prevents the deleterious effects of perinatal NMDAR-blockade. CypD-deficient animals are protected from loss of PVI immunoreactivity and altered synaptic activity on these neurons. In addition they do not exhibit deficits in rule-shifting, novel-object recognition, and social interaction. Thus, CypD activation and subsequent mitochondrial ROS release may be a potential novel mechanism that contributes to the pathological loss of PVI in schizophrenia.

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Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.09

Topic: A.07. Developmental Disorders

Title: Increased availability of acetyl-CoA in the cytosol results in synaptic dysfunction and an autistic-like phenotype in the mouse

Authors: *M. RIGBY[1], N. OREFICE[1], H. MITCHELL[2], A. FRELKA[3], R. PEARCE[3], L. PUGLIELLI[1];
[1]Med., [2]Waisman Ctr. IDD Models Core, [3]Anesthesiol., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Import of acetyl-CoA into the endoplasmic reticulum (ER) lumen by AT-1/SLC33A1 regulates the proteostatic functions of the organelle and the efficiency of the secretory pathway. Homozygous and heterozygous mutations affecting *AT-1* are associated with developmental delay and hereditary forms of sensory and autonomic neuropathy. In contrast, duplication of *AT-*

1 is associated with autism spectrum disorder (ASD), intellectual disability, and dysmorphism. Mice with reduced or increased AT-1 activity mimic associated human diseases. In particular, neuron-specific overexpression of AT-1 (AT-1 nTg) results in increased dendritic spine and branch formation, defects in synaptic plasticity, and autistic-like behavior. We recently discovered that AT-1 acts in concert with SLC25A1 and SLC13A5 to maintain intracellular acetyl-CoA flux. SLC25A1 is a mitochondria membrane transporter; it transfers citrate from the mitochondria lumen to the cytosol. In contrast, SLC13A5 is a plasma membrane transporter; it transfers citrate from the extracellular *milieu* to the cytosol. In the cytosol, citrate is converted to acetyl-CoA by ACLY and then transferred to the ER lumen by AT-1. Importantly, gene duplication events of *SLC25A1* and *SLC13A5* are also associated with ASD and intellectual disability. Here, we report the generation of mice with neuron-specific overexpression of either SLC25A1 (SLC25A1 nTg) or SLC13A5 (SLC13A5 nTg). As expected, the animals displayed increased cytosolic levels of both citrate and acetyl-CoA. Behavior testing revealed several common abnormalities, including cognitive and social deficits, aberrant jumping, and hyperactivity. Brain slice electrophysiology of SLC25A1 nTg mice showed enhanced long-term potentiation and diminished long-term depression. Similar experiments with SLC13A5 are on-going. Overall, the SLC25A1 nTg and SLC13A5 nTg phenotype is reminiscent of the AT-1 nTg phenotype, thus suggesting that perturbations in acetyl-CoA flux within neurons via increased activity of SLC25A1, SLC13A5, or AT-1/SLC33A1 can dramatically alter neuronal development and function to drive the development of ASD.

Disclosures: **M. Rigby:** None. **N. Orefice:** None. **H. Mitchell:** None. **A. Frelka:** None. **R. Pearce:** None. **L. Puglielli:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.10

Topic: A.07. Developmental Disorders

Support: NIH Grant GM111667-01
CSCRF 16-RMB-YALE-04
Kavli Foundation
KRIBB/KRCF research initiative program (NAP-09-3)

Title: Investigating human cortical developmental disorder using cortical organoids

Authors: *I.-H. PARK[1], Y. XIANG[3], Y. TANAKA[2], B. CAKIR[1], B. PATTERSON[1], Y.-J. KANG[4], S.-H. LEE[5];
[2]Genet., [1]Yale Univ., New Haven, CT; [3]Dept. of Genetics, Yale Sch. of Med., New Haven, CT; [4]Dept. of Neurol., [5]Neurol., Univ. of Arkansas For Med. Sci., Little Rock, AR

Abstract: Human brain organoid techniques have rapidly advanced to facilitate investigating human brain development and diseases. These efforts have largely focused on generating telencephalon due to its direct relevance in a variety of forebrain disorders. Despite its importance as a relay hub between cortex and peripheral tissues, the investigation of threedimensional (3D) organoid models for the human thalamus has not yet been explored. Here, we describe a method to differentiate human pluripotent stem cells (hPSCs) to cortical and subcortical organoids that specifically recapitulate the development of dorsal and ventral cortex, and thalamus. We applied the techniques to investigate human brain developmental disorders, called Rett syndrome (RTT) that are caused by mutations in MeCP2. Single-cell RNA sequencing revealed a formation of distinct cell types. Importantly, we made fusion of the distinct organoids to create the reciprocal interaction of cortical and subcortical regions. Our study provides a platform for understanding human cortical and subcortical development, and modeling circuit organizations and related disorders in the brain.

Disclosures: I. Park: None. **Y. Xiang:** None. **Y. Tanaka:** None. **B. Cakir:** None. **B. Patterson:** None. **Y. Kang:** None. **S. Lee:** None.

Nanosymposium

535. Neurodevelopmental Disorders: New Molecular Mechanisms

Location: Room N427

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 535.11

Topic: A.07. Developmental Disorders

Title: Modeling brain overgrowth in autism using human pluripotent stem cells

Authors: *S. CHETTY;
Stanford Univ., Stanford, CA

Abstract: A number of psychiatric disorders, such as autism and schizophrenia, are associated with severe mental impairments and disturbances, social and behavioral deficits, and poor cognitive abilities. Severe cases of these disorders are frequently associated with alterations in brain growth and size. Changes in brain structure and size precede the onset of clinical symptoms, suggesting that understanding the mechanisms regulating brain growth could provide a window of opportunity for early intervention. Directed differentiation of human induced pluripotent stem cells (hiPSCs) is a promising approach for disease modeling. Here, we generate hiPSCs from patients with psychiatric disorders associated with brain overgrowth or undergrowth. We differentiate patient-specific hiPSC lines into various neuronal and glial lineages and investigate the molecular and cellular mechanisms contributing to changes in brain size. Following differentiation into the neuronal and glial lineages, we identify cell types in the brain that are especially prone to alterations in cell proliferation, survival, and elimination. Our results show an important role for the neuroimmune system in regulating these cellular changes.

Signaling pathways that are commonly associated with controlling proliferation and pruning in early neurodevelopment are particularly deregulated in individuals with brain overgrowth. We show that cells that should be eliminated fail to undergo cellular elimination. Based on these mechanistic insights, we identify novel therapeutic targets for regulating cellular elimination and ultimately brain size in psychiatric disorders.

Disclosures: S. Chetty: None.

Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

Location: Room S401

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 536.01

Topic: B.11. Glial Mechanisms

Support: SFARI Grant 488574

Title: Glia-neuron interactions in *C. elegans*

Authors: S. RAIDERS[1], E. C. BLACK[1], A. BAE[2,3], S. SHAHAM[3], ***A. SINGHVI**[1,3];
[1]Fred Hutchinson Cancer Res. Ctr., Seattle, WA; [2]Albert Einstein Col. of Med., New York, NY; [3]Lab. of Developmental Genet., The Rockefeller Univ., New York, NY

Abstract: Glial pruning of neuron-endings in the mammalian central nervous system is implicated in control of synapse numbers during development, learning and memory, and aging. In vertebrate retina, RPE glia-like cells also engulf photoreceptor outer-segments. In *Drosophila,* glial engulfment of neuron fragments mediates axon pruning and developmental remodeling during metamorphosis. Disrupted glial pruning is associated with neurodevelopmental disorders such as autism, neurodegenerative disorders such as Alzheimer's disease and retinal degeneration. Engulfment by astrocytes in mice and *Drosophila* is mediated by the phagocytosis gene MEGF-10/Draper/ CED-1.
We report here that like glia in other species, glia in the nematode *C. elegans* engulf fragments of an associated neuron-ending. Thus, this critical glial function is evolutionarily conserved in *C. elegans* and can be interrogated in this invertebrate genetic model. The AFD is the primary thermo-sensory neuron of *C. elegans* with its microvilli sensory-ending embedded within a glial cell called amphid sheath (AMsh). The development of AMsh and AFD, and their glia-neuron contact site, are invariant across animals. Briefly, we found that when the sensory-ending of the AFD is labeled with GFP, punctate GFP fluorescence is also observed in the associated AMsh glia. We show that the AMsh glial staining is taken up from AFD neuron-endings and is abrogated in animals missing AFD neurons or with defective AFD neuron-endings. We will present our quantitative, (chemo)genetic and kinetic analyses of glia puncta which together show that glial engulfment is regulated by AFD activity throughout animal life.

To identify molecular mechanisms regulating glial engulfment, we performed also genetic screens which uncovered over sixteen mutants. Our analyses of some of these find that AMsh glia employ components of the phagocytic machinery, which mediates clearance of apoptotic cell corpses during animal development, to also engulf fragments of living AFD neurons. Surprisingly however, this machinery in *C. elegans* AMsh glia is not activated downstream of CED-1/MEGF10/Draper1, but instead a different receptor we have identified.
We previously showed that AMsh glia regulate shape and function of AFD-endings by regulating their ionic microenvironment and described the underlying molecular pathway (Singhvi et al, Cell, 2016). Together, our studies show that an individual *C. elegans* glia engages multiple molecular mechanisms to interact with a single associated neuron. Our experimental model allows us to systematically perform genetic analyses to probe interactions between these pathways.

Disclosures: S. Raiders: None. **E.C. Black:** None. **A. Bae:** None. **S. Shaham:** None. **A. Singhvi:** None.

Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

Location: Room S401

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 536.02

Topic: B.11. Glial Mechanisms

Support: Wayne State University Department of Pharmacology Research Stimulation Fund

Title: Novel role of ubiquitin specific protease 22 in glial-neuronal interactions during *Drosophila* development

Authors: *S. V. TODI, **W.-L. TSOU**;
Dept. of Pharmacol., Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: Delicate control of gene expression during neuronal development requires cooperation between histone modifications and transcriptional regulations. SAGA (Spt-Ada-Gcn5 acetyltransferase) is a multi-protein complex that plays an important role in modifying chromatin at various developmental and adult stages. In developing neuronal tissue, it is unclear how SAGA components are differentially required. Here, we tested the importance of individual SAGA components during the development of the fruit fly, *Drosophila melanogaster*. Our targeted efforts found that different components of SAGA are differentially important in neuronal vs. glial tissue in the fly. Of particular interest, the deubiquitinase, ubiquitin-specific protease 22 (USP22) is critical during larval development. Mutating USP22 or knocking it down specifically in glial cells leads to a remarkably delayed pupation rate in *Drosophila*; the time required for a larva to become a pupa is extended from the normal range of 7 days to nearly 56

days (an adult fly can live up to ~100 days). Targeting of other SAGA components did not have the same effect and the USP22 effect is glial-specific. Fly pupation is regulated by the release of the hormone, ecdysone, which binds to its receptors and enables larval transition into pupae. Feeding USP22-glial-knockdown larvae with ecdysone accelerated pupation, suggesting that ecdysone receptors are present. Ecdysone secretion by the prothoracic gland is under the control of the prothoracicotropic hormone, produced by neuroendocrine cells in the fly brain. Our additional findings suggest that glial USP22 regulates neuroendocrine cell development, potentially through insulin receptor- and AKT-dependent mechanisms. Our ongoing studies are further detailing the mechanism of what seems to be a SAGA-independent role for USP22 in glial-neuronal interaction during development.

Disclosures: S.V. Todi: None. **W. Tsou:** None.

Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

Location: Room S401

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 536.03

Topic: B.11. Glial Mechanisms

Support: NIH Grant F31NA100259
NIH Grant R01NS075062

Title: Bdnf signaling through TrkB.T1 is a novel mechanism for astrocyte morphological maturation

Authors: *L. M. HOLT[1,2], R. HERNANDEZ[1], N. L. PACHECO[2], M. HOSSAIN[1], M. L. OLSEN[1];
[1]Sch. of Neurosci., Virginia Tech., Blacksburg, VA; [2]Cell, Developmental, and Integrative Biol., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Brain derived neurotrophic factor (BDNF) is a critical growth factor involved in the maturation of neurons, including neuronal morphology and synapse refinement. Herein, we demonstrate astrocytes express high levels of BDNF's receptor, TrkB, with nearly exclusive expression of the truncated isoform, TrkB.T1 which peaks in expression during astrocyte morphological maturation. Using a novel astrocyte culture system, we show that astrocyte morphological complexity is increased in the presence of BDNF and loss of the TrkB.T1 receptor inhibits BDNF's effects of astrocyte morphology. Global or astrocyte-specific deletion of TrkB.T1 *in vivo* revealed morphologically immature astrocytes with significantly reduced volume and branching complexity, as well as dysregulated expression of perisynaptic genes associated with mature astrocyte functions, including synaptogenic genes. Indicating a role for functional astrocyte maturation via BDNF/TrkB.T1 signaling, TrkB.T1 KO astrocytes do not

support normal excitatory synaptogenesis. These data together suggest a significant role for BDNF/TrkB.T1 signaling in astrocyte morphological maturation, a critical process for CNS development.

Disclosures: L.M. Holt: None. **R. Hernandez:** None. **N.L. Pacheco:** None. **M. Hossain:** None. **M.L. Olsen:** None.

Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

Location: Room S401

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 536.04

Topic: B.11. Glial Mechanisms

Title: Monosynaptic tracing maps brainwide afferent oligodendrocyte precursor cell connectivity

Authors: *B. YALCIN, C. MOUNT, K. CUNLIFFE-KOEHLER, M. MONJE;
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Abstract: Neurons form both excitatory and inhibitory synapses with oligodendrocyte precursor cells (OPCs), but the circuit context of these “axon-glial” synapses is under-explored. Neuronal activity regulates OPC proliferation, oligodendrogenesis and myelin sheath structure in adulthood. These activity-regulated responses of oligodendroglial cells confer adaptive changes in motor function and influence some forms of cognition. Such plasticity of myelin has drawn attention to axon-glial synapses as a line of communication by which OPCs could adapt to activity-dependent neuronal signals. However, no afferent neuronal projections to OPCs have been mapped, hence our understanding of the neuronal territories accessed by these neuron-OPC synapses has been limited. Here, we employ a modified rabies virus-based monosynaptic tracing strategy to elucidate a map of neuronal synaptic connectivity to OPCs in the sensorimotor system *in vivo*. We identified extensive afferent synaptic inputs that primarily arise from functionally-interconnecting sensorimotor cortical areas and thalamic nuclei. OPCs residing in secondary motor cortex and underlying corpus callosum of adult mice receive comprehensive afferent connectivity from motor cortex and thalamic motor nuclei, demonstrating that motor system OPCs have synaptic access to brain-wide projection networks engaged in planning and execution of motor tasks. Similarly, mapping inputs to primary sensory cortex OPCs demonstrate inputs from functionally-interconnected sensory cortex and thalamic sensory nuclei. Deprivation of input activity to barrel field OPCs by whisker trimming does not alter the synaptic input ratios of surviving cells, nor does it impact the distribution of neuronal inputs. Taken together, these findings demonstrate that OPCs have strikingly comprehensive and remarkably stable synaptic access to brain-wide functionally-related network projections.

Disclosures: **B. Yalcin:** None. **C. Mount:** None. **K. Cunliffe-Koehler:** None. **M. Monje:** None.

Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

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Presentation Number: 536.05

Topic: B.11. Glial Mechanisms

Support: Diaser Foundation
Private donation

Title: The role of ectosomes in the patterning of the myelinated axon: Structural findings

Authors: ***S. SZUCHET**[1], S. A. .O'SULLIVAN[1], M. S. DOMOWICZ[2];
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Abstract: For vertebrates to exist and evolve, an energy efficient mechanism of fast nerve conduction had to be developed. The structure that fulfils this need, and hence sustains the very existence of the vertebrate kingdom, is the myelinated axon, whose modular architecture underlies saltatory conduction. Previous studies have revealed and characterized specific protein complexes populating the different axonal domains whose formation and positioning are critical for proper nervous system function. Studies have also uncovered neuronal-oligodendrocyte (OLG) cross-talk as essential for the formation of the modular architecture of the myelinated axon. However, how all of this is coordinated and executed is still unknown. Previous research from our laboratory has revealed a novel method of myelin sheath formation in the CNS. A number of new and critical concepts evolved from these studies. Based on these findings, we initiated a developmental study of the avian optic nerve, encompassing embryonic day (E) 12 to E21 and have established a time course that begins with OLG processes on their path to finding a neuronal partner and culminates in mature, compact myelination. We used transmission electron microscopy (TEM) and three-dimensional (3D)-electron tomography to investigate the initial phases of OLG/neuron interaction prior to myelin sheath formation. We present structural evidence that: i) upon reaching an axon, the OLG process splits into two branches that surround and embrace the axon, thereby positioning its plasma membrane directly around the axolemma; ii) within a circumscribed area, OLG and neuronal plasma membranes emit ectosomes. As ectosomes are known to be carriers of signalling molecules between cells in both prokaryotes and higher eukaryotes, we hypothesize that OLGs and neurons use ectosomes to communicate with one another, in order to coordinate, and implement the modular organization of the myelinated axon. The concept of ectosomes as potential custodians of active signalling molecules, that guide OLG-neuron interaction, marks a critical turning point in understanding the singularity of their interaction and cooperation. For now, the signalling molecules can be

identified by establishing first, the timing of ectosome release during development, followed by their purification and content characterization. Deciphering the code of OLG-neuron cross-talk will advance our knowledge of their intercellular communication under physiological conditions and pave the way for unravelling disease-specific biomarkers.

Disclosures: S. Szuchet: None. **S.A. .O'Sullivan:** None. **M.S. Domowicz:** None.

Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

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Presentation Number: 536.06

Topic: B.11. Glial Mechanisms

Support: NCI 1R01CA223388

Title: Progression of cortical hypersynchrony and epileptogenesis induced by brain tumors

Authors: *J. F. MEYER[1], K. YU[2], A. HATCHER[1], I. AIBA[1], B. DENEEN[2], J. L. NOEBELS[2]; [1]Neurol., [2]Baylor Col. of Med., Houston, TX

Abstract: Epileptic seizures are the most common presenting early symptom in several types of glioma, and they are often resistant to pharmacological treatment and even resection of the main tumor mass. Using a novel CRISPR/Cas9 glioma model that recapitulates the human disease more faithfully than previous xenograft models, we can study the disease from early symptoms to its final stages. To dissect the natural progression of tumor-related network hyperexcitability, we follow invasion of malignant glia populations into the surrounding cortical tissue and measure calcium activity of neurons using chronic EEG recording with two complementary *in vivo* imaging methods: two-photon microscopy to measure calcium activity in single neurons while tracking the morphology and location of nearby tumor cells over time, and widefield, one-photon imaging at >100 Hz to uncover changes in spontaneous and evoked aggregate, bilateral cortical activity of cell ensembles in the vicinity of the tumor mass and up to >5 mm beyond the tumor margin. At P40, we inject AAV-hsyn-GCaMP7f into a CRISPR-Cas9 mouse whose malignant astrocytes genetically express tdTomato and GCaMP7f for morphological and calcium wave visualization. Widefield imaging reveals progressive synchronization of aggregate activity across several millimeters of cortical areas starting at ~P70, with concomitant spiking activity on the EEG. Two-photon imaging of the same areas shows diverse cellular activity profiles that range from tight coupling to the EEG spike signatures to variable or even uncorrelated firing patterns. At this early stage of the disease, malignant astrocytes have only started invading the superficial cortical layers, and we observe their continuous proliferation and invasion as abnormal EEG events and cortical synchronization become more pronounced. Seizures typically did not appear until P100, when we observed spontaneous, severe seizures that manifested

electrographically, and optically in the calcium signal. In summary, this study reveals, for the first time, the spatial and temporal evolution of cortical epileptogenesis in a novel genetic brain tumor model using chronic imaging and simultaneous EEG and behavioral recordings.

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Nanosymposium

536. Molecular and Genetic Mechanisms Underlying Glia-Neuron Interactions

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Support: National Key R&D Program of China (2017YFC1307500, 2017YFC1307504)
National Natural Science Foundation of China (No. 81471249, 81622041, 81820108026)

Title: Immune-neuron interaction in radiation-associated cognition dysfunction

Authors: *J. CHENG[1], Z. SHI[1], J. JIANG[1], B. HE[1], Y. PEI[1], M. WU[1], H. CHEN[1], X. HU[2], J. XIE[1], W.-J. LIN[1], Y. TANG[1];
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Abstract: Radiotherapy enables long-term control or cure for patients with primary or metastatic head and neck tumors. However, around 50-90% of the patients suffer from cognitive dysfunction, and the underlying mechanism remains unclear. Our preliminary data showed that neuroinflammation is one of the main pathological features of radiation-induced brain injury (RIBI), which was corresponding to the degree of brain lesion and cognitive impairment. To identify the dynamic changes of cell types that may involve in the pathogenesis of RIBI, we applied single-cell RNA sequencing (scRNA seq) to analyze brain tissue samples collected from surgical specimen of RIBI patient. Our results revealed that microglia were the most affected cell type in the RIBI brains as compared with non-radiation control. The finding was further supported by the immunohistochemical staining results, in which the microglia were indeed significantly activated after radiation, with enlarged cell body and increased signal of the activation marker of CD68. Through further clustering analysis of scRNA seq data, we found that microglia showed high heterogeneity. Specific disease-associated microglia clusters expressing high APOE, Trem2, SPP, TYROBP were detected and confirmed by additional set of clinical samples analyzed by real-time PCR and immunohistochemical staining. In addition, using *in vivo* two-photon imaging, an increase of spine elimination and decrease of spine formation as well as decrease of calcium activity were seen in the cortex of mice after receiving single dose of 30Gy X-ray whole brain radiation. Notably, the expression of postsynaptic

markers PSD95 was also significantly reduced after radiation. All the neuronal changes were relevant to the memory deficit found in RIBI mouse model, as revealed by the object recognition test. Our results suggest that the radiation-induced microglia activation may play a critical role in dendritic spine remodeling and radiation-associated cognitive impairment. Our study indicates a novel mechanism of immune-neuron interaction in the cognitive dysfunction after radiation, which may inform new strategies for developing preventive and therapeutic treatment for RIBI.

Disclosures: **J. Cheng:** None. **Z. Shi:** None. **J. Jiang:** None. **B. He:** None. **Y. Pei:** None. **M. Wu:** None. **H. Chen:** None. **X. Hu:** None. **J. Xie:** None. **W. Lin:** None. **Y. Tang:** None.

Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

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Presentation Number: 537.01

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS083054
VA Merit award I01BX003033

Title: Cinnamon and its metabolite sodium benzoate upregulates astroglial GDNF via CREB and alleviates Parkinsonian pathology in the MPTP-lesioned mice

Authors: *D. PATEL[1], A. JANA[2], A. ROY[1,3], K. PAHAN[1,3];
[1]Neurolog. Sci., Rush Univ. Med. Ctr., Chicago, IL; [2]Dept. of Med., Univ. of Illinois, Chicago, IL; [3]Div. of Res. and Develop., Jesse Brown Veterans Affairs Med. Ctr., Chicago, IL

Abstract: Glial cell line-derived neurotrophic factor (GDNF) is known to promote the dopaminergic (DA) neuronal survival in cellular and animal models of Parkinson’s disease (PD). However, ectopic GDNF delivery either by stereotactic injection or viral overexpression is associated with long lasting adverse side effects in PD patients. Therefore, finding a safer and more effective approach to exploit the neuroprotective effects of GDNF remains an active area of research in developing a treatment to inhibit the PD progression. Previously, we reported that cinnamon, a commonly-used spice and sodium benzoate (NaB), a cinnamon metabolite, a food-additive and a FDA-approved drug against hyperammonemia, are capable of upregulating neuroprotective molecules (Parkin and DJ-1) and protecting the nigrostriatum in MPTP induced mouse model of PD. In this study, we describe that cinnamon and NaB are also capable of upregulating astroglial GDNF. We validated our findings through battery of biochemical arrays, using primary mice astrocytes, human astrocytes and cell specific conditional knockout mice that lack endogenous GDNF from the astrocytes (G*dnf* $^{\Delta astro}$ mice). Notably, NaB stimulated the mRNA and protein expression of GDNF in primary mouse astrocytes and human astrocytes. Furthermore, oral administration of cinnamon and NaB increased the astroglial GDNF

expression in the nigra of normal as well as MPTP-intoxicated mice. Signaling mechanisms for driving the upregulation of GDNF in astrocytes are poorly understand. Earlier, we reported that NaB is capable of inducing the activation of CREB in both astrocytes and neurons via protein kinase A. Here, we investigated the role of CREB in NaB-mediated upregulation of GDNF in astrocytes. Presence of cAMP response element (CRE) in the *Gdnf* promoter, recruitment of CREB to the *Gdnf* promoter by NaB and abrogation of NaB-mediated GDNF expression by siRNA knockdown of CREB suggested that NaB induces the transcription of *Gdnf* via CREB. At functional and therapeutic level, we noticed that oral administration of cinnamon and NaB protected tyrosine hydroxylase (TH) positive neurons in the substantia nigra pars compacta (SNpc) and fibers in the striatum, normalized striatal neurotransmitters, and improved the locomotor activities in MPTP-intoxicated G*fap* ^{cre} mice but failed to render the similar effects in *Gdnf* $^{\Delta astro}$ mice. Together, these findings highlight the importance of astroglial GDNF in cinnamon and NaB-mediated protection of the nigrostriatum in MPTP mouse model of PD and suggest possible therapeutic potential of cinnamon and NaB in PD patients.

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Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 537.02

Topic: C.03. Parkinson’s Disease

Title: Multi-kinase inhibition may have optimal effects on neurodegenerative pathologies via the tyrosine kinase discoidin domain receptors (DDRs)

Authors: *A. J. FOWLER, M. HEBRON, A. A. MISSNER, J. D. GREENZAID, X. LIU, C. E. H. MOUSSA;
Neurol., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Many neurodegenerative diseases share the feature that there is an accumulation of proteins which become neurotoxic. For example, amyloid-β; or tau in Alzheimer’s Disease (AD), α-synuclein in Parkinson’s disease (PD), or an overlapping of these proteins in Dementia with Lewy bodies (DLB). Although there have been a number of studies which explored targeting these neurotoxic proteins at their various stages of production and dysfunction none so far has led to a successful therapy for use in humans. Tyrosine kinases (TK) have increased activation in multiple neurodegenerative diseases including AD and PD. Specific TKs, Abelson (All) and Discoidin Domain Receptors 1 and 2 (DDR) are upregulated in the midbrain and hippocampus in post-mortem PD and AD brains, respectively. We have shown in preclinical models that Nilotinib, an Abl inhibitor, penetrates the brain and activates parkin leading to Beclin-1 mediated autophagic clearance of aggregated α-synuclein. In the A53T mouse model of

α-synucleinopathy we have shown that knockdown of DDR2 via shRNA leads to a reduction in the levels of α-synuclein, inflammation, and microglial activity without a change in cell number. LCB-03-0110, a reported potent DDR inhibitor, inhibits DDR1 and DDR2 activation *in vitro*. In the triple mutant APP mouse, a low dose of LCB reduced amyloid-β;, phosphorylated tau, microglia, astrocytes, and increased cognition. In a viral-vector gene-transfer model, where human α-synuclein is expressed in the substantia nigra of C57BL/6J mice, a low dose of LCB decreased α-synuclein load and improved behavior in these animals. Next, we evaluated the efficacy of a novel derivative of LCB, CM101, for its safety and toxicity, and its ability to reduce protein load in vitro and in vivo. Future studies aim to continue to understand the role of DDRs in neurodegeneration and develop LCB and CM101 as a potential new therapies.

Disclosures: A.J. Fowler: None. **M. Hebron:** None. **A.A. Missner:** None. **J.D. Greenzaid:** None. **X. Liu:** None. **C.E.H. Moussa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder.

Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

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Presentation Number: 537.03

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS097643

Title: Effect of LRRK2 kinase inhibition and G2019S-LRRK2 expression in a rat a-synuclein fibril model of Parkinson’s disease

Authors: *K. J. KELLY[1], V. DELIC[2], S. CHANDRA[3], H. J. SCOTT[3], A. B. WEST[1]; [1]Pharmacol. and Cancer Biol., Duke Univ., Durham, NC; [2]Res. & Develop., Veterans Affairs | New Jersey Hlth. Care Syst., East Orange, NJ; [3]Neurol., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Parkinson’s disease (PD) is a progressive movement disorder pathologically characterized by the presence of α-synuclein inclusions throughout much of the brain in late stages of disease and a dramatic loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in mid stages of disease. PD is usually sporadic although there are genetic forms, of which the G2019S mutation in the l*eucine-rich repeat kinase 2* (LRRK2) gene is one of the most common. All pathogenic mutations in *LRRK2* that can cause PD have been shown to increase kinase activities, and different experimental models *in vitro* in cultured cells, in invertebrates, as well as in mice, suggest LRRK2 mediates some forms of α-synuclein aggregation and neurotoxicity. It is thought that increased LRRK2 kinase activity may

exacerbate α-synuclein neurotoxicity. Therefore, developing a strategy to reduce LRRK2 kinase activity may be beneficial in reducing α-synuclein inclusion burden and neurodegeneration. Herein we evaluated two structurally similar compounds but with different pharmacokinetic profiles, PF475 and PF360, in a α-synuclein pre-formed fibril model in non-transgenic outbred rats. Rats were stereotactically injected with α-synuclein pre-formed fibrils (PFFs) into the SNpc and neurotoxicity was evaluated three months post injection, a time we previously demonstrated to include both abundant inclusions in the SNpc, striatum, along with dopaminergic neurodegeneration. Rats treated with the kinase inhibitor PF-475 for six weeks at 30 mg/kg OG BID significantly rescued SNpc dopamine neurons but did not alter α-synuclein deposition into inclusions. In contrast, in-diet dosing with PF-360 (avg. ~10 mg/kg daily) with similar LRRK2 inhibition as the PF-475 dosing regimen did not result in neuroprotection or prevention of inclusions. Further, the expression of G2019S-LRRK2 in Sprague-Dawley rats (Taconic) from a human BAC transgene did not affect fibril-induced neurodegeneration or inclusions. We continue to evaluate novel LRRK2 kinase inhibitors and associated efficacies in α-synuclein model systems to help clarify the tentative relationship between LRRK2 kinase activity and α-synuclein induced neurodegeneration.

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537. Molecular Targets for Parkinson's Disease: Animal Models

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Presentation Number: 537.04

Topic: C.03. Parkinson’s Disease

Support: Intramural funds of the National Institute on Drug Abuse

Title: G-protein biased dopamine D3R agonist modulates D1R-D3R interactions to attenuate β-arrestin signaling pathways in levodopa induced dyskinesia

Authors: W. XU[1], X. GUITART[2], B. CAMPOS[2], W. REA[2], S. FERRÉ[2], ***S. KORTAGERE**[1]; [1]Drexel Univ. Col. of Med., Philadelphia, PA; [2]Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Parkinson’s disease (PD) is the second most common age-related disease involving degenerating dopamine nerve function. Although dopaminergic treatments can be effective for moderating disease related loss of motor function, their utility is limited by long term treatment effects such as Levodopa induced dyskinesia (LID). While several hypotheses have been proposed to understand the role of D3Rs, its effects on other receptors and their signaling pathways, studies have been limited due to lack of selective D3R ligands. We have recently developed SK609, a G-protein biased signaling agonist of D3R and demonstrated its efficacy in

improving the motor symptoms of PD in a rodent model. In addition, SK609 under chronic treatment conditions does not produce dyskinesia side effects and when co-administered with Levodopa blocks abnormal involuntary movements associated with LID. These behavioral observations have led us to hypothesize that SK609 modulates LID by targeting the interactions of D3R with D1R and their respective signaling pathways in the striatum. To test this hypothesis, we have used the rodent model of LID and chronic SK609 treatment. Our preliminary results indicate that SK609 regulates the membrane expression of D3R and D1R in striatum. In addition, SK609 significantly reduced the expression of β-arrrestin 2, while it upregulated phosphorylated AKT levels in striatum of LID rats. In reserpinized mice, SK609 did not increase locomotor activity in combination with D1R agonists, but synergistically upregulated phosphorylated AKT levels in these mice. Current studies are aimed at understanding the differences in mechanism of biased and unbiased agonists of D3Rs in modulating D1R-D3R interactions and their signaling partners under LID conditions. We anticipate that biased signaling agonists of D3Rs can provide an opportunity to treat PD and LID while limiting other side effects seen with most dopaminergic agents.

Disclosures: **W. Xu:** None. **X. Guitart:** None. **B. Campos:** None. **W. Rea:** None. **S. Ferré:** None. **S. Kortagere:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Polycore Therapeutics LLC.

Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

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Presentation Number: 537.05

Topic: C.03. Parkinson’s Disease

Support: East Carolina University Startup

Title: Role of Nurr1 in environmental regulation of the dopaminergic phenotype

Authors: H. S. PARTINGTON, J. M. NUTTER, *J. B. EELLS;
Anat. and Cell Biol., East Carolina Univ. Sch. of Med., Greenville, NC

Abstract: The nuclear receptor Nurr1 is necessary, in ventral midbrain dopamine neurons, for development and maintenance of dopamine neurotransmission. Mutations in Nurr1 have been implicated in various dopamine related neurologic and neuropsychiatric disorders including addiction, depression, schizophrenia and Parkinson’s disease. Based on previous research, environmental stimuli in adult mice, such as stress, mating, exercise, environmental enrichment, and changes in circadian cycle, can increase or decrease the number of dopamine neurons. For example, 14 days of exercise and environmental enrichment increases the number of midbrain dopamine neurons by ~15%. Additionally, 7 days in a male-female pair increases dopamine

neurons in males but decreases them in females. Based on this data, our hypothesis is that Nurr1 will be important in this process of changing the dopamine neuron phenotype, with reduced Nurr1 attenuating induction of the dopamine neuron phenotype and exacerbating the loss of the dopamine neuron phenotype. To test this hypothesis, Nurr1-null heterozygous and wild-type mice were divided into treatment groups consisting of exercise (access to running wheel and running for 14d) and control mice and another treatment group consisting of mice placed in male/female pairs or control mice in same sex pairs for 7 d. Tissue was collected and the number of dopamine neurons, based on tyrosine hydroxylase immunoreactivity, and Nurr1 immunoreactive neurons will be measured. Using images acquired with the Celldiscover7, the number of labeled neurons across treatment groups will be counted. For accurate, unbiased cell counts, images will be collected in Z-stacks of the middle 80% of the measured thickness of each section in order to avoid overlap. Using Zeiss image deconvolution and extended depth of focus, we can obtain near-confocal quality images for cell counts. Based on preliminary data, we have identified a subpopulation of neurons in the ventral midbrain in wild-type mice that are Nurr1 immunoreactive ($Nurr1^{IR}$) but lack tyrosine hydroxylase immunoreactivity ($TH^{negative}$). Current studies are ongoing, but this data suggests that these $Nurr1^{IR}/TH^{negative}$ neurons may represent a latent population of dopamine neurons that have the potential to be induced to a dopamine phenotype. Understanding the molecular mechanisms associated with how dopamine neurons change their phenotype could be useful for treatment of diseases associated with dopamine neurotransmission.

Disclosures: H.S. Partington: None. **J.M. Nutter:** None. **J.B. Eells:** None.

Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

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Topic: C.03. Parkinson’s Disease

Support: Cure Parkinson's Trust 021006
Dr Gordon is supported by an Advance Queensland Fellowship AQRF03116-17RD2
Wesley Medical Research Project 2016-37

Title: Bruton's tyrosine kinase (BTK) regulates inflammasome activation and neuropathology in Parkinson’s disease

Authors: *R. GORDON[1], N. BIRCH[1], K. HANTON[1], W. GODFREY[1], N. GROVES[1], J. D. O'SULLIVAN[2];
[1]Med., The Univ. of Queensland, Brisbane, Australia; [2]Neurol., Royal Brisbane and Women's Hosp. (RBWH), Brisbane, Australia

Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disorder worldwide. PD is characterised by a progressive loss of nigrostriatal dopaminergic neurons and the accumulation of α-synuclein aggregates in the form of Lewy-bodies. PD manifests as a debilitating spectrum of motor and non-motor deficits for which there are currently no effective treatments to slow or halt disease progression. Chronic immune and inflammasome activation underlies PD pathology. Neuroinflammation can be observed early in the disease process and still strongly evident in post-mortem analyses of PD patient brains. Persistent immune activation has thus been closely linked to disease progression based on a wealth of accumulating evidence in clinical studies and experimental models. Inhibition of the NLRP3 inflammasome has recently been shown to prevent α-synuclein pathology and dopaminergic neurodegeneration, indicating its potential as a disease-modifying therapeutic target for PD (Gordon et al., Science Translational Medicine 2018). The specific mechanism by which the NLRP3 inflammasome is activated in PD are yet to be elucidated. Herein, we demonstrate that Bruton’s Tyrosine Kinase (BTK), a member of the TEC family, is activated by pathological synuclein and triggers NLRP3 inflammasome activation in microglia. BTK is also activated in the nigrostriatal system of experimental PD models at the same time points as NLRP3 activation. Pharmacological inhibition of BTK signalling prevented inflammasome activation in primary microglia. Additionally, daily oral dosing with BTK inhibitors effectively reduces NLRP3 inflammasome activation markers and neuropathology in pre-clinical models of PD. Together, our results indicate that BTK could be a potential druggable therapeutic target to mitigate inflammasome activation and neuropathology in PD.

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Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

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Presentation Number: 537.07

Topic: C.03. Parkinson’s Disease

Support: NIH: R21AG059391

Title: Prevention of intra- and extracellular α-synuclein toxicity and seeding by single domain antibodies

Authors: *E. E. CONGDON[1], Y. LIN[1], E. M. SIGURDSSON[1,2];
[1]Neurosci. and Physiol., [2]Psychiatry, New York Univ. Sch. of Med., New York, NY

Abstract: Immunotherapy represents one of the most promising avenues for treating neurodegenerative diseases characterized by protein aggregates, including Parkinson’s disease

(PD), and other synucleinopathies. A major challenge facing any CNS therapeutic is achieving sufficient brain penetrance for efficacy. One potential solution is the use of camelid single domain antibodies (sdAbs). These antibody fragments (13 kDa) offer several advantages over mAbs (150 kDa), including smaller size and the ability to recognize cryptic epitopes. We conducted a screen of a large number of sdAbs derived from a llama immunized with human α-synuclein (αsyn). Based on their binding to various forms of αsyn, several of these were then tested for efficacy in preventing αsyn-induced toxicity and pathological seeding.
For these experiments we prepared primary neuronal cultures from wild type (wt) and A53T transgenic mice, which express mutated human αsyn. In previous studies using anti-tau mAbs, we simulated two different potential mechanisms of action, extra- and intracellular blockage/clearance. Likewise, αsyn enriched from PD and the anti-αsyn sdAbs were added either together (αsyn + sdAb) or the sdAb 24 h after αsyn (αsyn → sdAb). In the former approach, the αsyn and sdAb primarily interact extracellularly, and intracellularly in the latter approach. Addition of αsyn alone in wt cells induced significant toxicity as measured by GAPDH levels (41% reduction, $p < 0.0001$), and in those cultures six different sdAbs prevented toxicity under both dosing conditions. In A53T cells, similar αsyn-induced toxicity was seen (46% GAPDH reduction, $p < 0.0001$), in addition to seeding of αsyn in the remaining cells (αsyn levels 4.5-fold above untreated control cells, $p = 0.0003$). When the sdAbs were used in the αsyn + sdAb condition, three of them prevented toxicity (93, 113, 171% of control values, $p = 0.002$, $p < 0.0001$, $p < 0.0001$). All but one of the sdAbs were effective in preventing αsyn seeding. In the αsyn → sdAb paradigm, three of the six sdAbs prevented αsyn toxicity (171, 86, 106% of control values, $p < 0.0001$, $p = 0.02$, $p < 0.0001$ respectively). As before, all but one were effective in preventing αsyn seeding. Interestingly, efficacy of individual sdAbs did not entirely overlap between dosing paradigms, likely due to differences in uptake and binding.
These results demonstrate the intra- and extracellular therapeutic potential of anti-αsyn sdAbs, and further highlight the disconnect that can occur between protein seeding and toxicity. Ideally, both parameters should be incorporated into each efficacy assay, which often focus only on the seeding component.

Disclosures: **E.E. Congdon:** None. **Y. Lin:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I am an inventor on a patent application assigned to NYU covering the sequences of the sdAb clones..

Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 537.08

Topic: C.03. Parkinson’s Disease

Support: Henan state research support grant 42318

Title: Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Parkinson's disease animal models

Authors: *C. HOLSCHER;
Neurosci. Drug Discovery Group, Henan Univ. of Chinese Med., Zhengzhou, China

Abstract: Aims: Recently, a phase II double blind placebo controlled clinical trial showed good protective effects of the glucagon-like peptide 1 (GLP-1) receptor agonist Exendin-4 (Bydureon) in patients with Parkinson's disease (PD). We have tested newer GLP-1 mimetics in animal models of PD and they showed superior effects to exendin-4. We also have shown that glucose-dependent insulinotropic polypeptide (GIP) analogues have good neuroprotective effects in PD mouse models. Novel dual GLP-1/GIP receptor agonists have been developed to treat diabetes and they show superior effects to single GLP-1 mimetics. We tested four different dual GLP-1/GIP agonists in rodent models of PD. Methods: Dual agonists were tested at equal doses to compare effects in the MPTP mouse model of PD and the 6-OHDA rat model of PD. The GLP-1 analogue Exendin-4 was tested along for comparison. NLY01, a pegylated form of exendin-4 that is currently being developed as a treatment for PD, was also tested. Motor activity, TH expression in the striatum and substantia nigra, chronic inflammation in the brain, oxidative stress and the levels of alpha-synuclein, pro-inflammatory cytokines and growth factors in the brain were measured. N=8 per group, all animals were male.Results: It was found that two of the novel GLP-1/GIP agonists (DA4-DA5) that have been optimized to cross the blood-brain-barrier were superior to exendin-4 and other dual agonists. The pegylated version of exendin-4 NLY01 showed the poorest efficacy, most likely because it cannot cross the BBB. In a direct comparison in the MPTP mouse model, DA-JC4 and DA-CH5 were best in protecting motor activity, TH expression, reducing chronic inflammation, levels of pro-inflammatory cytokines, levels of alpha-synuclein, and enhancing GDNF and BDNF levels in the brain. Conclusion: The novel dual agonists DA-JC4 and DA-CH5 show great promise in protecting the brain from PD like neurodegenerative processes and may be superior to exendin-4 in the clinic.

Disclosures: C. Holscher: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Nanosymposium

537. Molecular Targets for Parkinson's Disease: Animal Models

Location: Room S104

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 537.09

Topic: C.03. Parkinson's Disease

Support: Fundação de Amparo a Pesquisa do Estado de Sao Paulo;

Conselho Nacional de pesquisa
Coordenação de Aperfeiçoamento de Pessoal

Title: Repositioning of tetracycline as modulators of L-DOPA-induced dyskinesia

Authors: M. BORTOLANZA[1], G. CRIVELARO DO NASCIMENTO[1,2], C. FONTANARI[2], L. H. FACCIOLI[2,3], R. RAISMAN-VOZARI[3], ***E. DEL BEL**[1];
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Abstract: Inflammatory mechanisms are proposed to play a role in L-DOPA-induced dyskinesia in Parkinson's disease.. Herein we characterize the effect of the semi-synthetic second-generation tetracyclines, antibiotics with ancillary neuroprotective effects, doxycycline, minocycline and the non-antibiotic tetracycline COL-3 in parkinsonian rats presenting L-DOPA-induced-dyskinesia. Rats sustained unilateral injections of 6-hydroxydopamine into the medial forebrain bundle receive L-DOPA for 14 days. To evaluate how tetracyclines affect the dyskinesia, L-DOPA primed rats received an acute i.p. injection of doxycycline or minocycline or intracerebroventricularly COL-3. Another group of parkinsonian rats were chronically treated with L-DOPA concomitantly with either doxycycline or minocycline. Acutely administered doxycycline, minocycline or COL-3 attenuated established dyskinesia. The co-treatment of L-DOPA with doxycycline or minocycline and L-DOPA suppressed the development of dyskinesia without compromising the motor benefits of L-DOPA. The anti-dyskinetic effect of doxycycline was associated with a decreased expression of astrocyte, microglia, cyclooxygenase-2, matrix metalloproteinase and the production of reactive oxygen species. The anti-dyskinesia outline was accompanied by a serum decrease of PGE-2 and NOx. Pearson correlation revealed that MMP2/MMP9 gelatinolytic activity, MMP3 expression, reactive oxygen species, NOx and PGE2 were factors with a strong positive correlation with intensity of L-DOPA-induced-dyskinesia. This study revealed a notable anti-dyskinetic effect of the tetracycline derivatives modifying the behavioral and molecular consequences of L-DOPA treatment of hemiparkinsonian rats. Based on tetracycline excellent safety profiles in humans (use for over 50 years as antibiotics), we propose the repurposing of the tetracycline derivatives as an adjunctive therapy to treat L-DOPA-induced dyskinesia.

Disclosures: M. Bortolanza: None. **G. Crivelaro do Nascimento:** None. **C. Fontanari:** None. **L.H. Faccioli:** None. **R. Raisman-Vozari:** None. **E. Del Bel:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.01

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Title: HSF1 and tumor suppressor p53, a dangerous relationship in Huntington's disease

Authors: N. L. ZARATE[1], T. A. INTIHAR[1], D. YU[1], E. A. MARTINEZ[2], ***R. GOMEZ-PASTOR**[1];
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Abstract: Huntington’s disease (HD) is a neurodegenerative disorder characterized by motor and cognitive decline due to the progressive loss of medium spiny neurons (MSNs) in the striatum. HD is caused by an expanded CAG repeat in the *HTT* gene, leading to HTT protein misfolding and aggregation. We showed that Heat shock transcription factor 1 (HSF1), critical for the regulation of protein folding machinery, energy metabolism and synapse formation, is degraded in HD, contributing to MSNs death and HD pathology.
Understanding the mechanism behind HSF1 degradation is critical to design effective therapies to restore HSF1 levels in MSNs and ameliorate disease. HSF1 is degraded by sequential phosphorylation and ubiquitylation reactions mediated by protein kinase (CK2α’) and the E3 ligase Fbxw7 respectively. Both CK2α’ and Fbxw7 are transcriptionally up-regulated in MSNs of the zQ175 HD mouse model, in human iPSCs differentiated into MSN-like cells and in the striatum of patients with HD. The mechanism responsible for the up-regulation of these two genes and therefore the degradation of HSF1 is still uncharacterized. Via *in silico* analyses of CK2α’ and Fbxw7 gene sequences, we observed the presence of putative regulatory binding sites for the tumor suppressor p53. p53 is up-regulated in HD and it has been previously implicated in the HD pathology due to its role in mediating mitochondrial dysfunction, although the mechanism behind this effect is unclear. We now show that p53 is up-regulated in MSNs in HD mice where CK2α’ and Fbxw7 are induced. Using chromatin immunoprecipitation, we demonstrated that p53 binds to CK2α’ and Fbxw7 gene sequences and that such binding is enhanced in HD striatal-like cells. p53 pharmacological inhibition (Pifithrin-α) and siRNA treatments resulted in down-regulation of CK2α’ and Fbxw7, increased HSF1 protein levels and DNA binding-activity and improved mitochondrial function. Our work demonstrates the possible role of p53 as an upstream component of the HSF1 degradation pathway in HD and provides a mechanistic link between p53, HSF1 degradation and mitochondrial dysfunction in HD.

Disclosures: **N.L. Zarate:** None. **T.A. Intihar:** None. **D. Yu:** None. **E.A. Martinez:** None. **R. Gomez-Pastor:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.02

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Field Neurosciences Institute
John G.Kulhavi Professorship in Neuroscience at CMU

Title: Solid lipid curcumin particles improved learning and memory and protected medium spiny neurons morphology in YAC128 mouse model of Huntington's disease

Authors: *A. AL-GHARAIBEH[1,2,3], R. CULVER[2,3], S. J. HEILEMAN[2,3], B. SRINAGESHWAR[2,3,4], D. STORY[2,3,5], K. SPELDE[2], L. PALADUGU[2,3], N. MUNRO[2,3,4], N. MUHN[2,3], N. KOLLI[2], J. ROSSIGNOL[2,3,4], P. MAITI[2,3,5,7], G. L. DUNBAR[6];
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Abstract: Huntington’s disease (HD) is a genetic neurodegenerative disease characterized by motor, cognitive, and psychiatric symptoms, accompanied by massive neuronal degeneration in striata. In this study, we utilized solid lipid curcumin particles (SLCPs) to test their efficacy as a treatment for deficits in the YAC128 HD mouse model. We treated YAC128 male and female mice at 11 months of age every other day by oral gavage of 100 mg/kg of SLCPs, solid lipid particles (SLPs) or vehicles (PBS) for 8 weeks, and measured their motor performance on the accelerating rotarod every other week for 8 weeks, and their learning and memory performance in an active avoidance task during week 8. The mice were euthanized, and their brains were utilized for Golgi-Cox staining to study the morphology of MSNs, or for immunohistochemistry to measure numbers of microglia and astrocytes, or Western blotting to quantify amounts of DARPP-32, BDNF, TrkB synaptophysin, PSD-95, LAMP-2, CD86 and CD163. We found that both SLCPs and SLPs improved learning and memory in HD mice as measured by the active avoidance tasks. We also found that SLCP treatment preserved MSNs arborization and spinal density, and decreased cortical inflammation compared to HD control groups. SLP treatment also showed a profound effect on decreasing inflammation in HD brains compared to HD vehicle controls. Our results indicate that SLCPs or SLPs produce therapeutic effects in HD mice, and suggest that earlier treatment could enhance therapeutic efficacy

Disclosures: A. Al-Gharaibeh: None. **R. Culver:** None. **S.J. Heileman:** None. **B. Srinageshwar:** None. **D. Story:** None. **K. Spelde:** None. **L. Paladugu:** None. **N. Munro:** None. **N. Muhn:** None. **N. Kolli:** None. **J. Rossignol:** None. **P. Maiti:** None. **G.L. Dunbar:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.03

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: R01 1R01NS095441
Cure Alzheimer's Fund Grant

Title: Dietary salt induces cognitive impairment by promoting tau pathology

Authors: *G. FARACO[1], K. HOCHRAINER[1], S. G. SEGARRA[1], S. SCHAEFFER[1], M. M. SANTISTEBAN[1], A. MENON[1], H. JIANG[2], D. M. HOLTZMAN[2], J. ANRATHER[1], C. IADECOLA[1];
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Abstract: High dietary salt promotes cognitive impairment independently of hypertension. In mice, high salt diet (HSD) impairs the endothelial regulation of microvascular flow and lowers cerebral blood flow, effects associated with profound cognitive impairment (Nat Neurosci, 21:240, 2018). However, how endothelial dysfunction leads to cognitive impairment is unclear. Since, accumulation of phosphorylated tau, a microtubule associated protein linked to Alzheimer's disease, has been linked to vascular cognitive impairment and endothelial dysfunction, we tested the hypothesis that HSD affects cognition through tau phosphorylation. C57BL/6 mice were fed HSD (8% NaCl) or normal diet (ND; 0.5% NaCl) for 12 weeks. HSD increased tau phosphorylation at $Ser^{202}Thr^{205}$ (AT8) and Thr^{231} (RZ3) in both neocortex and hippocampus. Immunohistochemistry showed AT8 immunoreactivity in neuronal cell bodies of the somatosensory and pyriform cortex. Furthermore, consistent with an increase in insoluble tau, HSD increased tau in both RIPA and formic acid soluble fraction. However, neurofibrillary tangles were not observed. Administration of L-Arg, which restores endothelial and cognitive function (Nat Neurosci, 21:240, 2018), prevented the HSD-induced increase in tau phosphorylation. Since Cdk5 is a major kinase mediating tau phosphorylation and reduced endothelial NO may induce cleavage of p35 into p25 by calpain and activation of Cdk5 via p25 (Austin, Circ Res., 2016), we examined if HSD influences calpain and Cdk5 activity. HSD increased the catalytic activity of both calpain and Cdk5, whereas L-Arg administration suppressed the activity of both enzymes, further implicating a deficit in endothelial NO in the effects of HSD on tau. In addition, administration of the inhibitory Cdk5 peptide TFP5 suppressed AT8 and RZ3 levels in neocortex and hippocampus and improved cognitive function in HSD mice. Consistent with the involvement of a deficit in endothelial NO, we found that HSD reduces calpain nitrosylation, which suppress the activity of the enzyme (Hypertension, 71:761, 2018). HSD-induced cognitive impairment was not observed in $Tau^{-/-}$ mice and after treatment of WT mice with anti-tau antibodies (HJ8.8), providing evidence that tau pathology is critical for the HSD-induced cognitive dysfunction. Remarkably, cognitive function was rescued despite persistence of hypoperfusion suggesting that the reduction in cerebral blood flow is not sufficient to induce cognitive impairment. The findings unveil a previously-unrecognized link between

dietary habits, vascular dysfunction and tau pathology with potential implications for both vascular and cognitive health.

Disclosures: **G. Faraco:** None. **K. Hochrainer:** None. **S.G. Segarra:** None. **S. Schaeffer:** None. **M.M. Santisteban:** None. **A. Menon:** None. **H. Jiang:** None. **D.M. Holtzman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C2N Diagnostics, AbbVie. F. Consulting Fees (e.g., advisory boards); C2N Diagnostics, Denali, Genentech, and Proclara. **J. Anrather:** None. **C. Iadecola:** F. Consulting Fees (e.g., advisory boards); Broadview Ventures.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.04

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: Scully Initiative
Taube Family Foundation
Jean Perkins Foundation
Horngren Family

Title: Modulating p75 neurotrophin receptor signaling alleviates synaptic degeneration and dysfunction in a mouse model of tauopathy

Authors: *A. LATIF-HERNANDEZ[1], T. YANG[1], K. C. TRAN[1], H. LIU[1], S. M. MASSA[2], F. M. LONGO[1];
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Abstract: Tau has important physiological roles in excitatory synapses; however, increasing evidence from mouse models and postmortem AD studies indicates that alterations of tau function may mediate synaptic dysfunction and subsequent synapse loss, which is the most consistent pathological correlate of cognitive decline in AD. Under stimulus paradigms promoting hippocampal long-term plasticity, activity-dependent tau translocation is concomitant with changes in the postsynaptic protein content, that lead to increases in PSD95, glutamatergic AMPA receptor GluA1, actin and Fyn kinase levels. In pathological conditions, hyperphosphorylated tau translocates from microtubules to dendritic spines, leading to increases in Ca^{2+} influx and contributing to synaptic dysfunction by altering both trafficking and synaptic anchoring of glutamate receptors. In previous studies, we found that pharmacological modulation of the p75 neurotrophin receptor (p75 NTR) inhibits tau hyperphosphorylation as well as other potentially pathogenic tau post-translational modifications. Here, we tested the hypothesis that the p75 NTR modulator, LM11A-31, would prevent tau molecular pathology and mitigate

deficits in the generation of hippocampal plasticity. PS19 (P301S) mice were treated for 3-months by oral gavage with LM11A-31. Combining *ex vivo* acute hippocampal slices subjected to electrophysiological long-term potentiation (LTP) with protein immunoblotting and immunostaining, we investigated which molecular events govern the downstream effectors of postsynaptic phosphorylated tau that ultimately alter the mechanisms underlying synaptic plasticity. Our results in PS19 mice revealed reductions in levels of PSD95 and synaptophysin in hippocampal synaptosome preparations and deficits in LTP at Schaffer collateral synapses, concurrent with tau hyperphosphorylation. These deficits are attenuated by *in vivo* modulation of p75 NTR. In addition, LTP-related deficits are normalized in hippocampal potentiated slices taken from PS19 mice that were treated with LM11A-31, including activity-dependent activation of NR2B, decreases in CaMKII-β phosphorylation and reductions of GluA1 levels, in association with decreased levels of excess tau phosphorylation. These results support a role for p75 NTR modulation in preventing pathological tau phosphorylation and associated mechanisms that contribute to hippocampal synaptic deficits.

Disclosures: **A. Latif-Hernandez:** None. **T. Yang:** None. **K.C. Tran:** None. **H. Liu:** None. **S.M. Massa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PharmatrophiX. **F.M. Longo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PharmatrophiX.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.05

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: Alzheimer's Association NIRG-396905
NHMRC Project Grant 1105284

Title: Orexin receptor antagonist-induced effects on sleep, cognition and tau pathology in the rTg4510 mouse model of tauopathy

Authors: *R. J. KEENAN[1], L. CORNTHWAITE-DUNCAN[1], H. DAYKIN[1,2], S. OBERRAUCH[1], M. BRIAN[1], J. METHA[1], K. J. BARNHAM[2], G. ALLOCCA[1,2], D. HOYER[1,2,3], 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 tau aggregates. Sleep disruptions are

emerging as crucial aspects of these disorders, both as consequence and aggravator of tauopathy. Tau transgenic rTg4510 (rTg) mice express the human P301L *MAPT* mutation associated with FTD, which is suppressed by administration of doxycycline (DOX). We have shown previously that chronic DOX treatment rescues spatial memory deficits, reduces tau and phosphorylated tau (p-tau) levels and attenuates brain atrophy in rTg mice. rTg mice also exhibit a hyperarousal phenotype during the active phase and a REM sleep deficit during the inactive phase. The REM deficit was rescued by DOX treatment, whereas the hyperarousal phenotype was not altered. In the present study, we therefore used two orexin receptor antagonists MK-1064 (OX_2R selective) or suvorexant (OX_1R/OX_2R) to correct sleep-wake deficits in rTg mice and assess their influence on cognition and brain tau and p-tau levels.
4.5-month-old male and female WT and rTg mice were used. In Experiment 1, mice were orally administered suvorexant (50 mg/kg/day) during the inactive phase to increase REM sleep, or vehicle (0.5% methylcellulose), for 6 weeks (n = 14-16 per group). In Experiment 2, mice were orally administered MK-1064 (40 mg/kg/day) at the beginning of the active phase to replace hyperarousal with a balanced increase of NREM and REM sleep, or vehicle (20% TPGS), for 6 weeks (n = 16-19 per group). Four weeks into treatment EEG/EMG head-mounts were surgically implanted. Sleep was recorded at 6 months of age and analysed using Somnivore™. Cognition was then assessed in the Barnes maze before brain samples were collected.
Suvorexant treatment increased REM sleep post-dose, however, it did not affect Barnes maze performance nor alter brain tau or p-tau levels in rTg mice. MK-1064 treatment partially reduced wakefulness/hyperarousal and increased NREM and REM sleep post-dose. MK-1064 treated rTg mice also showed partial restoration of spatial memory recall in the Barnes maze compared with vehicle treated rTg mice. The effects of MK-1064 on brain tau and p-tau levels and further analyses assessing the relationship between sleep-wakefulness, tau and cognition will be presented.
In conclusion, restoring only REM sleep had no effect on cognition nor tau or p-tau levels in rTg mice. By contrast, reducing hyperarousal by increasing NREM and REM sleep during the active phase had beneficial cognitive effects, highlighting the importance of balanced sleep-wakefulness as a therapeutic target in tauopathy-related neurodegenerative disorders.

Disclosures: **R.J. Keenan:** None. **L. Cornthwaite-Duncan:** None. **H. Daykin:** None. **S. Oberrauch:** None. **M. Brian:** None. **J. Metha:** None. **K.J. Barnham:** None. **G. Allocca:** None. **D. Hoyer:** None. **L.H. Jacobson:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.06

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Title: Knock out of Trem2 exacerbates phenotypes in P301S tau transgenic mice

Authors: *A. F. FEITEN, A. VAN HUMMEL, J. VAN DER HOVEN, F. DELERUE, Y. D. KE, L. M. ITTNER;
Dementia Res. Ctr. and Dept. of Biomed. Sci., Macquarie Univ., Sydney, Australia

Abstract: Alzheimer's disease (AD) is characterised by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of the hyperphosphorylated microtubule associated protein tau. These two pathological hallmarks have been explored for decades however it remains not fully understood how they interact with each other and how they trigger disease onset and progression. Recently other genetic risk factors have been identified in genome wide association studies. One of these risk factors are polymorphisms of the triggering receptor expressed on myeloid cells 2 (TREM2). Thus far TREM2 has mostly been studied in the context of Aβ. The effects of TREM2 on tau pathology remain poorly understood and the current literature is conflicting. Here, we have examined the effect of TREM2 on tau pathology in an P301S tau transgenic mouse model, TAU58/2. TAU58/2 mice are characterized by an early onset and progressive NFT pathology and behavioural, motor and memory deficits. Our new TREM2 knockout (KO) mice were crossed with TAU58/2 transgenic mice and all genotypes were subjected to a variety of functional tests including rotarod, open field, elevated plus maze, beam, hanging wire and Morris water maze at 1,2,3 and 6 months of age. Brains were collected at these various time points and immunohistochemical and biochemical analysis performed. At 3 months of age TAU58/2 mice present with moderate motor deficits on the rotarod, this phenotype was significantly aggravated upon TREM2 reduction and complete depletion. Histological analysis revealed increased numbers of cells with tau phosphorylated at serine 422, a marker for late stage pathology. Interestingly, knock out of TREM2 impacted on motor performance as mice aged, independent of the presence of transgenic tau. Taken together, our results showed that reducing TREM2 exacerbates the functional deficits of TAU58/2 transgenic mice. Furthermore, we found an accelerated progression of tau phosphorylation. Hence, our work suggests that reduction and loss of TREM2 function contributes to functional deficits in AD also via augmenting tau pathology.

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Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.07

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: Canadian Institutes of Health Research, MOP-115056

Alzheimer's Society Canada
Weston Brain Institute
ASBMB - PROLAB Award

Title: Anxiety-related behavior, memory impairment and systemic insulin resistance in humanized tau mice

Authors: *R. A. GONÇALVES[1,2,4], N. WIJESEKARA[2], P. E. FRASER[2,3], F. G. DE FELICE[5]; [1]Ctr. for Neurosci. Studies, Queens Univ., Kingston, ON, Canada; [2]Tanz Ctr. for Res. in Neurodegenerative Dis., [3]Dept. of Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [4]Inst. of Med. Biochem. Leopoldo de Meis, Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil; [5]Fed Univ. Rio De Janeiro, Rio de Janeiro, Brazil

Abstract: Alzheimer's disease (AD) is historically recognized as a disease of memory but the neuropathological spectrum of this disease is complex with patients presenting other alterations, such as mood disorders and peripheral metabolic dysregulation. Microtubule-associated protein tau assists in polymerizing and stabilizing microtubules and Tau pathophysiology has been particularly implicated in Alzheimer's disease (AD). Our group has previously shown that tau ablation triggers severe glucose intolerance and pancreatic dysfunction in mice, suggesting that, tau may play a role in peripheral metabolism. However, the effects of tau ablation on mood-related behavior remains to be elucidated. Here, we evaluated memory, mood and systemic insulin resistance in 4-5 months old Wild Type (WT), mTau-/- and mTau-/- expressing the WT human Tau protein (hTau+/-mTau-/-). Anxiety-related behavior was assessed by the Open-Field and Zero Maze tasks. Tail-Suspension and Forced Swim tests were performed to assess behavior despair. Novel Object Recognition (NOR), Barnes Maze and Contextual and Cued Fear Conditioning were performed to evaluate cognition. Peripheral metabolic parameters were assessed by Insulin Tolerance Test (ITT - 1IU insulin/kg body weight, i.p.) and fasting plasma insulin and leptin levels by ELISA. Male and female mice were used in this study. Our findings demonstrate that systemic tau deletion in mice leads to anxiety-related behavior and impaired contextual and cued fear memory. The presence of a WT human Tau transgene in the hTau+/-mTau-/- mice did not ameliorate these phenotypes but impaired object recognition memory and aggravated systemic insulin sensitivity when compared to mTau-/- and WT animals. Our results suggest that tau protein plays a role in whole-body insulin sensitivity and anxiety-related behavior. Our findings also suggest that previously unrecognized functions for tau may be a complicating factor in using animal models on the mTau-/- background. Understanding the link between tau pathophysiology, mood disorders, and metabolic alterations is of great importance to establishing the complete contribution of tau protein to AD pathogenesis.

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Nanosymposium

538. Animal Models of Neurodegenerative Disorders

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Presentation Number: 538.08

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Mesenchymal stem cells protected Purkinje cells and recovered gait of a porcine model of ataxia-telangietasia

Authors: *P. NEGRAO DE ASSIS[1], D. KOTA[1], J. DYKSTRA[2], J. CAIN[3], J. WEIMER[1]; [1]Weimer Lab., [2]Sanford Res., Sioux Falls, SD; [3]Weimer Lab., Sanford Res., Sanford Research, SD

Abstract: Ataxia-telangiectasia (AT) is a rare autosomal recessive disease caused by mutations in the ATM gene. This disease currently does not have a cure. The hallmark symptoms are a progressive lack of motor coordination (ataxia) and enlargement of small blood vessels (telangiectasia) in the eyes and skin. Affected individuals have a compromised immune system and increased risk of cancer. Diabetes was also reported in AT patients. Arguably, the neurodegeneration is the aspect that most impacts the life quality of patients living with AT. The ataxia has an early childhood onset, and individuals require a wheelchair by adolescence. There is a severe neuronal loss in the cerebellum, specifically, of Purkinje cells (PC). Several murine models of AT were developed to study the disease, but no model fully recapitulated the neurological phenotype. Therefore, we used the first AT swine model, previously developed by our team, to study the motor deficit, damage in the PC layer, and a possible treatment with mesenchymal stem cells (MSCs). One group received one MSC injection at 90 days-old and another received four injections monthly, starting at 30 days-old. Cells were delivered intravenously and intranasally. Animals were tested monthly, from 180 until 450 days-old. Gait was measured using the Zeno Electronic Walkway (ZenoMetrics Peekskill, NY) customized for pigs. Data was processed with the PKMAS Software (Protokinetics LLC, Havertown, PA). To detect gait abnormalities, we analyzed 186 gait parameters and four body measurements using Principal Component Analysis (PCA). Additionally, we used immunohistochemistry (IHC) to assess damage in the cerebellum. Our results showed that MSCs successfully recovered gait deficits and protected the PCs. MSCs have anti-inflammatory properties yet not fully understood, and they are likely not capable of completely curing AT. However, MSCs are relatively easy to obtain and could improve the quality of life of AT patients.

Disclosures: P. Negrao De Assis: None. **D. Kota:** None. **J. Dykstra:** None. **J. Cain:** None. **J. Weimer:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.09

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Expression of mutant α-synuclein in oligodendrocytes induces remarkable glial inflammation and demyelination in the spinal cord and brainstem/cerebellar white matter: A novel model of multiple system atrophy-cerebellar type and primary progressive multiple sclerosis

Authors: *H. YAMAGUCHI[1], D. MATSUSE[1], K. MASAKI[1], T. SAIGA[1], Y. NISHIMURA[1], M. WATANABE[1], R. YAMASAKI[1], K. TANAKA[2], J.-I. KIRA[1];
[1]Dept. of Neurology, Neurolog. Inst, Kyushu Univ. Sch. of Med., Fukuoka, Japan; [2]Keio Univ. Sch. of Med. Dept. of Neuropsychiatry, Tokyo, Japan

Abstract: Aim: Multiple system atrophy (MSA) is classified to parkinsonian (MSA-P) and cerebellar (MSA-C) variants. The hallmark of MSA is α-synuclein (α-syn)$^+$ glial cytoplasmic inclusions in oligodendrocytes. Primary progressive multiple sclerosis (PPMS) is supposed to be caused by oligodendrocyte dystrophy. Accumulation of α-syn is also seen in glia and neurons in MS lesions. As there is no established animal models for MSA-C or PPMS, we aimed to develop a novel model of MSA-C and PPMS by overexpression of mutant α-syn in oligodendrocytes in a temporarily restrictive manner using Tet-off system. **Methods:** We generated and analyzed TetO-α-SynA53T Tg/+; PLP-tTA Tg/+ double transgenic mice (A53Tα-syn mice), which express mutant human A53Tα-syn in oligodendrocytes starting at 8 weeks of age when doxycycline was removed from the feed. **Results:** A53Tα-syn mice developed progressive mono-, hemi-, and paraparesis and ataxia around 22 weeks, culminating in death around 30 weeks. Human α-syn diffusely spread cerebellum, brainstem and spinal cord before the disease onset (at 16 weeks) while phosphorylated α-syn focally accumulated. Phosphorylated α-syn aggregated mainly in Nogo-A$^+$ oligodendrocytes showing loss of connexin (Cx)47 in the spinal cord and brainstem/cerebellar white matter. Focal demyelination and oligodendrocyte loss started from the phosphorylated α-syn-deposited areas, leading to widespread demyelination. In these lesions, increased GFAP$^+$ astrocytes showed extensive loss of Cx43 and Cx30, phagocytizing aggregated α-syn. Numerous Iba1$^+$ microglia expressing arginase-1 infiltrated, surrounding deposited phosphorylated α-syn. These lesions contained clusters of F4/80$^+$ macrophaeges and a few CD3$^+$ T cells. Gene ontology analysis using microarray data of the spinal cord revealed that differentially expressed genes were significantly enriched in immune system, and innate immune and inflammatory responses. Re-feeding of doxycycline at 23 weeks but not at 27 weeks recovered the neurological deficits. **Conclusion:** Our findings suggest that expression of mutant α-syn in oligodendrocytes induces remarkable glial inflammation and demyelination in the spinal cord and brainstem/cerebellar white matter, resembling MSA-C and partially PPMS.

Disclosures: H. Yamaguchi: None. **D. Matsuse:** None. **K. Masaki:** None. **T. Saiga:** None. **Y. Nishimura:** None. **M. Watanabe:** None. **R. Yamasaki:** None. **K. Tanaka:** None. **J. Kira:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

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Presentation Number: 538.10

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NAF SCA-YI
NIH U01 NS106670-01

Title: Longitudinal characterization of spinocerebellar ataxia type 3 mouse model CNS transcriptome

Authors: K. BLUMENSTEIN, A. ZALON, H. ZHANG, A. PIERCE, N. STEC, Y. GUAN, H. PAULSON, ***H. S. MCLOUGHLIN**;
Univ. of Michigan, Ann Arbor, MI

Abstract: Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph Disease (MJD), is the most common dominantly inherited ataxia in the world yet there is no effective treatment for this relentlessly progressive and fatal disease. With the goal of preventive therapy for SCA3, several recently completed or ongoing studies seek to reduce levels of the disease protein, including our recent study assessing the longitudinal efficacy of antisense oligonucleotide (ASO) therapy for SCA3. A necessary next step toward therapeutic success is a thorough assessment of SCA3 molecular changes over time, so that we can better understand potential neuroprotective pathways and identify promising biomarkers of disease. In our study, we compared transgenic SCA3 mice possessing the full-length human mutant *ATXN3* gene to wild type littermates. Through RNA sequencing (RNA-seq), we longitudinally characterized the central nervous system (CNS) transcriptome during early-, mid-, and late-stage of disease in two highly affected brain regions, the cerebellum and brainstem. By comparing diseased mouse data to wildtype littermate data over time, we uncovered changes in gene expression that are closely associated with, and possibly causally linked to, disease progression. Our findings revealed differential gene expression that exacerbates throughout disease progression, with the brainstem most affected. RNA-seq identified 37 and 5 differentially expressed (DE) genes shared among all three timepoints in the brainstem and cerebellum, respectively. RNA-seq also identified 228 and 12 DE genes that were significantly different only in the two latter age groups in the brainstem and cerebellum, respectively. We are currently applying weighted gene co-expression network analysis (WGCNA) to categorize gene sets that significantly correlate over time and are using ingenuity pathway analysis (IPA) to associate biological meaning. Overall, this global gene profiling over time, the first to be completed in this model, will help identify the molecular events underlying disease and may elucidate protective pathways and biomarkers for SCA3.

Disclosures: K. Blumenstein: None. **A. Zalon:** None. **H. Zhang:** None. **A. Pierce:** None. **N. Stec:** None. **Y. Guan:** None. **H. Paulson:** None. **H.S. McLoughlin:** None.

Nanosymposium

538. Animal Models of Neurodegenerative Disorders

Location: Room N426

Time: Tuesday, October 22, 2019, 1:00 PM - 3:45 PM

Presentation Number: 538.11

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant

Title: Gabaergic inhibitory interneurons as therapeutic target for spinocerebellar ataxia type 1

Authors: *C. EDAMAKANTI, J. GEORGE, M. MARTINA, P. OPAL;
Northwestern Univ., Chicago, IL

Abstract: Spinocerebellar ataxia type1 (SCA1) is an adult-onset neurodegenerative movement disorder caused by a pathogenic polyglutamine expansion (CAG repeat) in the protein Ataxin-1 (ATXN1). SCA1 is a condition characterized by progressive problem with movement. People with this condition initially experience problems with coordination and balance (ataxia). Main pathological hallmark of the disease is Purkinje cell loss in cerebellum. Since ATXN1 is a transcriptional regulator it is not surprising that transcriptional misregulation appears as the initiating pathogenic event— indeed occurring as early as the first week of postnatal life. It is still unclear whether pathogenic changes occur only in Purkinje cells (PCs), the cells that are especially vulnerable in the disease, or whether other cell types contribute to pathogenesis. Given the importance of this postnatal period for cerebellar development, we asked whether this region might be developmentally altered by mutant ATXN1. We found that mutant ATXN1 —through transcriptionally upregulating the sonic hedgehog pathway—stimulates the proliferation of a relatively understudied cerebellar stem cell niche (defined by prominin-1; also, called CD133). Because these stem cells differentiate into GABAergic interneurons (basket cells and stellate cells) in molecular layer, there is an exaggerated inhibitory synapse formation with Purkinje cells. We have also confirmed the exaggerated GABAerigc interneuron connections in human SCA1 patients. This leads to significant increase in GABAergic interneuron inhibition of PCs, disrupting cerebellar Purkinje cell function in a non-cell autonomous manner. Mutant ATXN1 thus alters the neural circuitry of the developing cerebellum, setting the stage for the later vulnerability of Purkinje cells in SCA1. To interfere with the excessive GABAergic inhibition, we activated the endocannabinoid system (known to tamp down GABAergic inhibition in cerebellum by acting on presynaptic release of GABA) using endocannabinoid receptor agonist. We found that treated SCA1 mice performed significantly better on rotarod assay than untreated mice. This is the first drug that shows such a dramatic and prompt symptomatic improvement. Cannabinoid agonists are already FDA-approved for several disorders and we are optimistic that this might lead to a novel therapeutic treatment for SCA1.

Disclosures: C. Edamakanti: None. **J. George:** None. **M. Martina:** None. **P. Opal:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.01

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: R01NS102006 NINDS

Title: Osteopontin (SPP1) expression in HIV-infected humanized mice suppresses microglial inflammation in the brain

Authors: F. MAHMUD, T. BOUCHER, Y. DU, E. GREIF, P. SYSA-SHAH, R. DANNALS, M. POMPER, K. METCALF PATE, C. LYONS, B. CARLSON, ***A. M. BROWN**;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: High levels of inflammation in the brain can induce behavioral and cognitive dysfunction, and neuropsychiatric disorders. While elevated levels of specific inflammatory factors have been associated with HIV infection, for many of these, direct evidence of their contribution to neuropathogenesis has not yet been shown. In this study, we investigated osteopontin (OPN, *SPP1*), a multifunctional proinflammatory protein that is elevated in several major disorders of the nervous system including multiple sclerosis, Alzheimer's Disease, Parkinson's, frontotempro dementia and NeuroHIV. Previous studies from our group showed that in post-mortem tissue of individuals with moderate to severe HIV-associated neurocognitive impairment, that OPN is elevated in the CSF, and in brain microglia and neurons as quantified by immunohistochemistry. In the context of HIV-infection *in vitro*, OPN enhances virus replication through two mechanisms: 1) by promoting cell-to-cell fusion, and 2) signaling through a NFkB-dependent pathway that activates the HIV promoter, increasing viral replication. These results suggest that high levels of OPN in the brain may exacerbate HIV injury. However, in contrast, cortical neurons treated with OPN are protected from HIV-mediated damage to neuritic processes and neurotoxicity. To clarify its role, and to test the hypothesis that OPN is required for HIV-induced neuroinflammation, we used NSG-CD34 humanized mice infected, or not with HIV-1, and inhibited OPN expression with functional, or mutant RNA aptamers. PET-imaging of mice with [^{11}C]DPA-713 to quantify binding to the translocator protein (TSPO), a marker of microglial activation, was performed at 12 weeks post-infection/aptamer treatment. While no significant differences in TSPO ligand binding were detected in uninfected mice in which OPN expression was knockdown or at normal levels, in HIV-infected mice with reduced OPN levels, TSPO binding was significantly higher in multiple brain regions. Immunohistochemical analyses of post-mortem brains confirmed the increases in TSPO receptor levels and the number of Iba^{+} mouse microglia. These results suggest that in the brain, OPN expression plays a role in dampening HIV-induced microglial activation.

Disclosures: **F. Mahmud:** None. **T. Boucher:** None. **Y. Du:** None. **E. Greif:** None. **P. Sysa-Shah:** None. **R. Dannals:** None. **M. Pomper:** None. **K. Metcalf Pate:** None. **C. Lyons:** None. **B. Carlson:** None. **A.M. Brown:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.02

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Pioneering Funding Award funded by Cure Alzheimer's Fund (CAF; H.C)

Title: Assessment of adverse neurotoxicity of BoNT/A by using an engineered human brain model

Authors: *G. AMBRIN[1], B. R. SINGH[2], H. CHO[3];
[1]Biomed. Engin. and Biotech., Univ. of Massachusetts, Dartmouth, N. Dartmouth, MA;
[2]2Institute of Advanced Sciences,, N. Dartmouth, MA; [3]UNC Charlotte, Charlotte, NC

Abstract: The phenomenal neurotoxicity, its high target specificity coupled with persistence of intoxication makes Botulinum neurotoxin (BoNT) a deadliest bio-weapon as well as an indispensable therapeutic tool. So far, its effects have been ignored in a central nervous system (CNS), as it was believed that it stayed at the injected site, but recent studies have confirmed its capability of retrograde transportation and transcytosis while maintaining its enzymatic properties. Even though BoNT/A has been approved by the USFDA for its use as drugs in various diseases, clinical cases are being reported of short-term memory loss and bad dreams upon treatment with BoNT/A. Our research focuses on the adverse toxicity by continual use of BoNT/A leading to neurodegeneration. The reactive astrocytes (A1) are implicated in inducing microgliosis (M2) mediated by the complement cascade with the decrease in Acetylcholine (Ach). The study evaluates the side effects of the exhaustive use of BoNT/A as a potential risk factor for synaptic impairment eventually leading to dementia. For the evaluation of the study, we employed our engineered human brain on chips facilitating the tripartite culture among human neurons, astrocytes and microglia. Our human brain models were treated with BoNT/A, multiple times (treatment duration of 5, 10, and 15 min with a recovery time of 2, 3, and 4 days). The concentration of BoNT/A used varied from 0.1 pM to 1 nM. The enzymatic activity of BoNT/A leads to subsequent decrease in Ach secretion with every treatment. By 5th treatment, this decrease in Ach results in severe astrogliosis, compelling the neurons into expressing C1q (4-fold increase), mediated by astrocyte-derived transforming growth factor β (TGFβ, 5-fold increase). We found TGFβ as one of the key regulators of neuronal C1q expression. The downstream pathway of complement cascade was confirmed by the cleavage of C3 opsonization with the fragments C3a and iC3b leading to the elimination of the target structures by

phagocytosis through C3 receptors on glial cell (C3R/Cd11b/TREM2). C3a (8-fold increase) and CCL2 (3-fold increase) initiate the recruitment and activation of microglia triggered by BoNT/A mediated by detrimental astrogliosis. The discovery provides a new insight into the pathway the BoNT/A might take and prevent any potential neurodegenerative diseases by its exhaustive use as drug or in the cosmetic industry which has by so far been ignored.

Disclosures: G. Ambrin: None. **B.R. Singh:** None. **H. Cho:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.03

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Proteogenomic analysis of microglia during LPS-induced acute inflammation

Authors: *A. CARTIER, B. YEUNG, J. MOYRON-QUIROZ, Q. GAO, K. NAZOR, T. HUANG, S. ZOU, M. TAM, P. TAYLOR;
Biolegend, San Diego, CA

Abstract: Microglia are the major tissue resident macrophages in the brain and spinal cord, and function as sentinels in maintaining CNS homeostasis. Dysregulation of these cells has been associated with neuropsychiatric and neurodegenerative disorders. A major limitation in understanding microglial contribution to cellular processes and their role in disease has been the lack of tools to specifically distinguish these cells from other myeloid cells. In an effort to produce a microglia-specific tool, we previously generated and validated a rat monoclonal antibody against a highly selective microglia marker P2RY12. This marker is known as a homeostatic protein, and its expression was shown to be down-regulated in pro-inflammatory microglia. To assess alterations in P2RY12 expression, we used an inflammation model based on LPS administration. Adult C57BL/6 mice of 7-8 weeks of age were injected with either PBS, low or high dosages of LPS daily for 4 days after which microglia were harvested from the brain. Isolated cells were co-stained with CD11b, CX3CR1, and P2RY12 as general markers for microglia. Flow cytometric quantification using live cells showed a significant increase in $CD11b^+$ cells in both low and high dose LPS treated mice compared to the control untreated group. Furthermore, low and high dose LPS injections led to a significant reduction in P2RY12 and CX3CR1 expression in these cells. These data are consistent with a decrease in P2RY12 expression under inflammatory conditions. On-going experiments address LPS-induced alterations in microglial morphology that occur in pro-inflammatory conditions. To gain better understanding of microglial function, we are currently assessing their proteogenomic profile using BioLegend's proprietary technology, TotalSeq™. Our technology allows simultaneous analysis of both the transcriptome and proteome at the single-cell level via single-cell RNA-

sequencing (scRNA-Seq). Ongoing experiments utilize a number of antibody-oligonucleotide conjugates, including P2RY12, CD11b, CD45, and CX3CR1, to analyze differentially expressed genes and proteins under normal and LPS-induced inflammation in mice. These studies will potentially help elucidate the diversity and physiology of microglia in response to systemic inflammation.

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Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.04

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Project grant (#P00023016) by Indena S.P.A, Italy and by Verdure Sciences (#P00022925) to GM and EG
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International Journal of Molecular Sciences 2019 Travel Award to EG

Title: The anti-inflammatory potential of curcumin preparations on activated glial cell numbers and morphology in the GFAP-IL6 mouse brain

Authors: *E. GYENGESI, F. ULLAH, R. ASGAROV, G. NEIDERMAYER, G. MUENCH; Western Sydney Univ., Penrith, Australia

Abstract: Chronic neuroinflammation is both a feature and a potential cause of many neurodegenerative diseases like Alzheimer's disease and dementia. In the GFAP-IL6 mouse model of chronic microglia activation, the murine IL-6 gene is expressed by astrocytes under the transcriptional control of the glial fibrillary acidic protein (GFAP) promoter, resulting in brain-specific overexpression of IL6, causing a significant increase in microglial and astroglial numbers, change in cellular morphology, and neurodegeneration. Curcumin has low toxicity and a high potency as a cytokine-suppressive anti-inflammatory drug that can penetrate into the CNS. Both Meriva curcumin phytosome (MCP) and Longvida curcumin with solid lipid particles (LC) are highly bioavailable and have anti-inflammatory effects in humans.
This study investigated the hypothesis, that curcumin formulations, MCP and LC can decrease glial activation in chronic neuroinflammation, measured by decreased glial cell numbers and altered morphology.
GFAP-IL6 mice and their wild type (WT) littermates were fed with curcumin (MCP or LC) and were compared to normal diet fed controls. Three doses of MCP (140mg/kg, 70mg/kg and

35mg/kg body weight per day (bw/d) were fed to 3 months old GFAP-IL6 and WT mice for one month. In addition, LC (60 mg/kg bw/d) was fed to 2 months old GFAP-IL6 and WT mice for 4 months. The total number of Iba-1^+ and $TSPO^+$ microglia, and $GFAP^+$ astrocytes were determined in the cerebellum and hippocampus by immunohistochemistry and unbiased stereology. Furthermore, the morphology of the glial cells was assessed by confocal microscopy and Sholl analysis.
GFAP-IL6 mice displayed a difference in microglial and astroglial numbers in both the cerebellum and the hippocampus and a different microglial morphology compared to WT mice, showing an increased soma size and perimeter. The most effective dose of MCP (140mg/kg bw/d) decreased the number of $Iba1^+$ microglia by 26.2% in the hippocampus and 48% in the cerebellum in the GFAP-IL6 mice compared to GFAP-Il6 mice on normal food. Additionally, $GFAP^+$ astrocyte numbers in the hippocampus of GFAP-IL6 mice were also decreased by 42%. Administration of LC has led to a significant reduction in neuroinflammatory markers, decreasing the number of $Iba1^+$ microglia by 25.88% in hippocampus but not in the cerebellum, and the $TSPO^+$ cells by 24.46% in hippocampus and by 31.37% in the cerebellum of the GFAP-IL6 mice.
Together, these data show that both the high bioavailability curcumin MCP in short term and LC in long term feeding is able to attenuate the inflammatory pathology and potentially reverse the detrimental effects of chronic glial activation.

Disclosures: E. Gyengesi: None. **F. Ullah:** None. **R. Asgarov:** None. **G. Neidermayer:** None. **G. Muench:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.05

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Plexxikon Inc.
University of Nebraska at Omaha Office of Research and Creative Activity

Title: Developmental difference in the astroglial response to chorda tympani transection is independent of microglia presence

Authors: *A. J. RIQUIER, S. I. SOLLARS;
Univ. of Nebraska at Omaha, Omaha, NE

Abstract: The rat gustatory system is an excellent model for examining variability in the capacity for injury-induced neural regeneration across development. Full regeneration occurs following transection of the gustatory chorda tympani nerve (CTX) in adulthood (> 40 days of

age; P40), while an identical injury at ≤ P10 (neonatal) results in profound and permanent loss of central innervation and peripheral innervated taste buds. Microglia and astrocytes are central nervous system glial cells that respond to injuries by increasing in quantity near damaged or degenerating tissue, assuming a reactive state and secreting various pro and anti-inflammatory cytokines which can both promote or inhibit injury recovery. We previously demonstrated developmental differences in the magnitude of the microglia response to CTX. Given established differences in the inflammatory profile of microglia across development, we hypothesized a comparable and related difference in the astrocyte response. In the current study, rats underwent CTX at either P10 or P50 and were treated with i.p. injections of the colony-stimulating factor 1 receptor inhibitor PLX5622 (Plexxikon Inc.) or a vehicle solution. Brains were collected and stained for microglia (Iba1), phagocytic microglia (CD68), and astrocytes (GFAP) 4 days post-injury. Consistent with our previous work, CD68-negative microglia increased in quantity around damaged chorda tympani fibers in the brainstem in both age conditions ($p < .05$) and the microglia response was significantly larger in the adult condition relative to the neonatal condition ($p < .05$). The lack of CD68-positive microglia indicates microglia are not responsible for phagocytosing debris in the CTX paradigm. CTX also induced an increase in astrocytes but, strikingly, the neonatal response was nearly 4-times the magnitude of the adult astrocyte response. While PLX5622 administration ablated microglia by >97% in both the neonatal and adult rat brain, this depletion had no impact on the astrocyte increase. These data suggest independent yet developmentally variable glial responses to CTX that correspond to differences in recovery outcomes.

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Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.06

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: 5R01NS096144
5R21OD025320
R01NS091519
MR0541

Title: Modulation of neuroinflammatory signals mitigates radiation-induced neurocognitive decline independent of hippocampal neurogenesis

Authors: ***S. GOKHAN**[1], V. CHITU[2], K. M. ARONSON[3], Y. M. ALTUN[4], N. P. BRODIN[3], E. STANLEY[5], M. F. MEHLER[7], W. A. TOMÉ[6];

[1]Neurol., Albert Einstein Coll Medici, Bronx, NY; [2]Developmental and Mol. Biol., [3]Radiation Oncology, [4]Neurol., [5]Dept. of Developmental and Mol. Biol., [6]Radiation Oncology, Neurol., Albert Einstein Col. of Med., Bronx, NY; [7]Dept Neurol, Neurosci, Psychiat, Albert Einstein Col. Med., Bronx, NY

Abstract: The results of the RTOG 0933 and NRG CC001 clinical trials have shown that physical sparing of the hippocampus during cranial irradiation (CI) promotes the preservation of memory functions at 4- and 6-months following therapy. The protection of neural stem cells (NSCs) residing within the subgranular zone (SGZ) of the dentate gyrus and the suppression of inflammation is thought to be underlying this protective effect. Indeed, the ablation of microglia (MG) through blockade of the CSF-1R or selective targeting of $CCR2^{+}$ macrophages using an appropriate CCR2 inhibitor leads to the retention of hippocampal-dependent cognitive abilities following CI. Inhibition of Colony stimulating factor 2 (CSF-2), a proinflammatory cytokine induced by tissue injury that promotes the proliferation and activation of microglia, may be a suitable alternative strategy to alleviate inflammation. Our studies have evaluated the effects of ablation of *Csf2* and also the inducible ablation of MG on the properties of neuroinflammation, neurogenesis and CI-associated cognitive impairments employing the requisite mouse models. Here, we demonstrate that preservation of cognitive functions following CI does not require ablation of MG. The reduction in neuroinflammation following *Csf2* ablation was sufficient to prevent CI-induced cognitive decline. Moreover, neither the ablation of MG nor the inhibition of *Csf2* prevented the deficit in neurogenesis, thereby suggesting that NSC-mediated SGZ neurogenesis is not required for the prevention of radiation-induced cognitive dysfunction. We have previously shown that MG display seminal roles in neural development and adult homeostasis and plasticity. Our present study demonstrates that selective modulation of MG-associated neuroinflammatory signaling without MG ablation is a novel therapeutic strategy to preserve cognitive functions following CI. These experimental observations have seminal implications for patients undergoing radiation therapy for tumors of the brain or head and neck in which the hippocampus is inevitably exposed to a high dose of radiation leading to potentially debilitating and possibly avoidable cognitive deficits.

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Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

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Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.07

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant AG050431

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Zenith Fellows Award ZEN-17-438829

Title: Aspirin upregulates IL-1Ra in glial cells via PPAR-alpha

Authors: *K. PAHAN, S. CHAKRABARTI, A. ROY, T. PROROK, D. R. PATEL, S. DASARATHY;
Neurolog. Sci., Rush Univ. Med. Ctr., Chicago, IL

Abstract: Neuroinflammation is being recognized as a hallmark of different neurodegenerative disorders. Accordingly, chronic inflammation caused by interleukin-1beta (IL-1β) plays an important role in the loss of neurons observed in various neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and Huntington's disease. In an inflammatory CNS, IL-1β binds to its high-affinity receptor, interleukin-1 receptor (IL-1R), and upregulates a number of intracellular signaling pathways either to cause cell death in neurons or to amplify inflammation in glial cells. Conversely, interleukin-1 receptor antagonist (IL-1Ra) binds to the same receptor and inhibits IL-1R-mediated signaling pathways. However, the pathways by which IL-1Ra could be upregulated in brain cells for suppressing neuroinflammation are poorly understood. Aspirin is a widely-used pain medication throughout the world and it is also showing promise beyond its known pain-relieving capacity. This study underlines a new property of aspirin in upregulating IL-1Ra in astrocytes and microglia. Aspirin upregulated the expression of *Il-1Ra* mRNA and protein in mouse astrocytes and microglial cells in both a time- and dose-dependent manner. While investigating mechanism, we found that *IL-1Ra* gene promoter harbors one consensus PPRE and that aspirin upregulated IL-1Ra in astrocytes isolated from PPARβ (-/-), but not PPARα (-/-), mice. Accordingly, aspirin increased IL-1Ra *in vivo* in the cortex of wild type and PPARβ (-/-), but not PPARα (-/-), mice. Similarly, aspirin treatment increased astroglial and microglial IL-1Ra in the cortex of FAD5X, but not FAD5X/PPARα (-/-), mice. Finally, recruitment of PPARα by aspirin to the peroxisome proliferator response element (PPRE) of the *IL-1Ra* promoter suggests that aspirin increases the transcription of *IL-1Ra* gene via PPARα. This study delineates a novel property of aspirin in increasing IL-1Ra in glial cells via PPARα and suggests that aspirin may find further therapeutic application in neuroinflammatory and neurodegenerative disorders. This study was supported by a merit award from Veteran Affairs (I01BX002174), the Zenith Fellows Award (ZEN-17-438829) from Alzheimer's Association and a grant (AG050431) from NIH.

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Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.08

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: AHA
NIH

Title: A comparison of microglial response and lesion resolution after intracerebral hemorrhage in young and aged mice

Authors: X. YANG, X. LIU, H. REN, J. WANG;
Anesthesiology/Critical Care Med., The Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Background and Purpose: Advancing age is one of the most common risk factors associated with intracerebral hemorrhage (ICH). However, research into age-related ICH has been insufficient, as young healthy animals are used in most preclinical studies. Our goal was to investigate how aging affects the lesion volume, resolution, and microglial phagocytic function in an ICH mouse model. **Methods:** We evaluated the lesion volume, resolution, and neurologic functional outcome after collagenase-induced striatal ICH in young and aged mice. The lesion volume and perihematomal edema were assessed by high magnetic field multimodel MRI scanning. Perihematomal brain tissue was collected and examined for expression of microglial marker Iba1 and the scavenger receptor CD68. We injected aged red blood cells from GFP-UBC mice to assess phagocytosis. **Results:** Functional outcome was worse in aged mice than in young mice on days 3 and 7 after ICH (n=12 mice/group, $p<0.05$). MRI scanning showed that aged animals had a larger lesion volume on days 3 and 7 and greater perihematomal edema on day 3 than did young animals (n = 6~8 mice/group, $p<0.05$). In addition, microglial phagocytic function was attenuated in aged animals when compared with that of the young animals on day 5 after injection of aged red blood cells (n=5 mice/group, $p<0.05$). **Conclusion:** Aged mice exhibit weakened microglial phagocytosis, delayed hematoma clearance, and worse functional outcome than do young mice. The findings illustrate the importance of studying ICH in models that include aged animals.

Disclosures: X. Yang: None. **X. Liu:** None. **H. Ren:** None. **J. Wang:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.09

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Hacettepe University Scientific Research Projects Coordination Unit (TSA-2017-14418)

Scientific and Technological Research Council of Turkey (118S435)

Title: Resolution of neuroinflammation triggered by cortical spreading depression

Authors: *Z. KAYA, N. BELDER, S. YILMAZ-OZCAN, B. DONMEZ-DEMIR, E. EREN-KOCAK, H. KARATAS-KURSUN, M. YEMİSCİ, T. DALKARA;
Inst. of Neurolog. Sci. and Psychiatry, Hacettepe Univ., Ankara, Turkey

Abstract: Migraine is a common disorder. Migraine pathophysiology needs deeper understanding in order to develop more effective drugs. Cortical spreading depression (CSD) is the neurophysiological correlate of migraine aura. The idea that "CSD-triggered migraine pain emerges as a result of parenchymal and subsequent meningeal sterile inflammatory response" is generally accepted. Upon opening of pannexin-1 channels in neurons by CSD, the formation of inflammasome complex, activation of caspase-1 and release of high-mobility group box 1 (HMGB1) are the key points that activate the pro-inflammatory NF-kappa B cascade in astrocytes. We hypothesized that the resolution of this sterile inflammation might have a role in the spontaneous cessation of migraine headache. This study investigates the resolution of inflammation mediated by caspase-1, HMGB1 and NF-kappa B p65 activation following a single CSD. A single CSD was induced by pinprick in male Swiss Albino mice. Brains were harvested 15 minutes, 1, 3 and 5 hours after CSD. Activation of caspase-1, HMGB1, and p65 was investigated using immunofluorescent labelling and Western blotting. The time course of caspase-1 activity was investigated by monitoring its cleaved active form. We found that caspase-1 activity significantly increased 1 and 3 hours after CSD and largely returned to basal level (sham) at 5 hours (n=3 at each time point and sham groups). However, HMGB1 release from the neuronal nuclei was still not restored 5 hours after CSD; approximately 25% of cortical nuclei did not exhibit HMGB1 immunoreactivity at 15 min and 5 hours after CSD (n=3 at each time point). Likewise, activation of p65 in non-neuronal cells, which was assessed by nuclear translocation of p65 in NeuN-negative cells, was found to be perpetuated when assessed 15 minutes and 5 hours after CSD (approximately 25% of non-neuronal cells, n=3 at each time point). No induction was found in p65 protein levels 3 hours after CSD as detected by Western blotting. In conclusion, although caspase-1 activity begins to decline in 5 hours, other components of inflammation are still active, suggesting that suppression of CSD-induced parenchymal inflammatory response may last longer than 5 hours. This raises the possibility that parenchyma may continue to drive the meningeal neurogenic inflammation for hours into the headache phase.

Disclosures: Z. Kaya: None. **N. Belder:** None. **S. Yilmaz-ozcan:** None. **B. Donmez-demir:** None. **E. Eren-kocak:** None. **H. Karatas-kursun:** None. **M. Yemİscİ:** None. **T. Dalkara:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.10

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Charlotte and Gwyneth Gray Foundation to Cure Batten Disease (https://www.curebatten.org) and Sanford Health.

Title: Cln6 deficient glia are primed for activation and contribute to the neuronal deficits observed in CLN6 Batten disease

Authors: *J. N. SHEETS, K. FRANCIS, J. WEIMER, J. CAIN;
Sanford Res., Sioux Falls, SD

Abstract: Batten disease, or neuronal ceroid lipofuscinoses (NCLs), represent a class of lysosomal storage disorders characterized by lysosomal dysfunction, cellular accumulation of storage material, and neurodegeneration. CLN6 Batten disease is a NCL variant caused by mutations in the *CLN6* gene encoding a transmembrane endoplasmic reticulum (ER) protein of unknown function. Emerging data has revealed a positive correlation between regions of neuronal loss and glial activation in *Cln6* models, suggesting that gliosis may contribute to pathogenesis. To identify the role of gliosis in the progression of CLN6 disease, cortical neurons and glia were harvested from Cln6^{nclf} mice at postnatal day 1-2 (P1-2) for *in vitro* analyses and probed for NCL pathological hallmarks. We identified a time-dependent increase in LysoTracker, ATP synthase subunit C, and autofluorescent storage material (ASM) intensity in *Cln6* compared to wild-type (WT). To determine the effects of gliosis on *Cln6* neuronal pathology, glia were isolated and activated by lipopolysaccharides (LPS) and interferon gamma (INF-γ). Glial activation demonstrated a marked increase in cell spreading, GFAP organization, and nuclear translocation of NF-κB and P-STAT1 in both astrocytes and microglia. Resting astrocytes and microglia isolated from *Cln6* deficient mice showed increased GFAP and CD68 expression, respectively, suggesting *Cln6* deficiency primes glia for activation independent of artificial activation. To determine the role of the astrocyte secretome on neuronal viability, arborization, and NCL hallmarks, neurons were incubated with astrocyte-conditioned media. Automated high-content image analyses revealed that conditioned media harvested from WT astrocytes inhibited neuronal NCL-associated protein accumulation, promoted neuronal viability, and normalized neurite outgrowth. These assays suggested the *Cln6* deficient astrocytic secretomes play a role in *Cln6* pathology. To identify *Cln6* effects on the astrocyte secretome, supernatants from WT and *Cln6* deficient astrocytes were assayed for inflammatory cytokines, revealing increased secretion of pro-inflammatory cytokines in *Cln6* deficient astrocytes when compared to WT astrocytes. Ongoing experiments are elucidating the functional effects of defined chemokines as well as determining the contact-mediated effects of astrocytes on *Cln6* neurons. Exploring the role of gliosis in CLN6 Batten disease may help identify drug targets for future treatment strategies or reveal novel signaling cascades that may lead to improved outcomes in Batten disease patients.

Disclosures: **J.N. Sheets:** None. **K. Francis:** None. **J. Weimer:** None. **J. Cain:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.11

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Lady Davis Institute / TD Bank Studentship Award
CIHR grant 103400

Title: The quaking RNA binding protein regulates alternative splicing in microglia during demyelination and remyelination in the CNS

Authors: *J.-S. LEE[1,2], X. CHEN[2], S. RICHARD[2,1];
[1]Biochem., McGill Univ., Montreal, QC, Canada; [2]Lady Davis Inst., Montreal, QC, Canada

Abstract: Microglia, the innate immune cells in the central nervous system (CNS), play crucial roles in maintaining CNS homeostasis, development, and inflammation. In the presence of injury or change in the brain homeostasis, microglia cells are activated and migrate towards the site of the event to release factors to orchestrate immunologic response. Activated microglia have been closely linked to progression of neurodegenerative diseases, however, its impact on pathogenesis remains ill-defined. Quaking (QKI) is an RNA binding protein expressed in glial cells such as oligodendrocytes and microglia. QKI plays a critical role in differentiation processes of these cells by altering mRNA splicing, stabilizing mRNA and regulating micro- and circular-RNA formation. However, the role of QKI in microglia function have not been investigated to date. Previously we generate a conditional allele of qkI and showed qkI regulates alternative splicing of many myelin genes in oligodendrocytes. Herein we generated a mouse model that specifically deletes QKI in microglia using $Cx3cr1^{CreERT2}QKI1^{fl/fl}$ mice. Depletion of QKI in microglia resulted in increased in the cell number with abnormal microglial morphology displayed by enlarged cell bodies with significant reduction in dendritic length. These microglia possessed dysregulated alternative splicing patterns in pre-mRNAs, defining for the first time a role for QKI in alternative splicing regulation in microglia. Since altered splicing could affect the characteristics of microglia, we further investigated the activation of microglia by analyzing inflammatory and phagocytotic markers. QKI deficient microglia cells showed significant upregulation of pro-inflammatory transcripts and exhibited increase in the TREM2 phagocytotic receptor consistent with our morphological data that QKI deficient microglia cells acquire an activated microglia phenotype. To understand how mice without QKI react to the loss of myelin, we used a 0.2% cuprizone diet to induce demyelination followed by remyelination. Five weeks of cuprizone induced the expected demyelination in the corpus callosum of both control (wild type) and QKI-deficient mice. When the cuprizone was removed from their diet, wild type mice remyelinated the corpus callosum as expected while the QKI deleted mice were unable to

remyelinate. Based on this cumulative evidence, our results show that QKI is an important regulator of alternative splicing in microglia especially during myelin regeneration. Jeesan Lee is a recipient of a Lady Davis Institute / TD Bank Studentship Award. This work is funded by a CIHR grant to Stéphane Richard.

Disclosures: **J. Lee:** None. **X. Chen:** None. **S. Richard:** None.

Nanosymposium

539. Neurotoxicity, Inflammation, and Neuroprotection

Location: Room S103

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 539.12

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

Support: AHA grant 14SDG20410063 (SAA)
Mayo Foundation

Title: Dysfunctional phenotype of microglia isolated from eNOS-/- mice

Authors: *S. A. AUSTIN, Z. S. KATUSIC;
Mayo Clin., Rochester, MN

Abstract: It is estimated that in 2018, 92 million Americans are living with some form of cardiovascular disease. Importantly, people with cardiovascular risk factors have a higher incidence of Alzheimer’s disease (AD). A common feature of cardiovascular disease risk factors is endothelial dysfunction defined by decreased bioavailability of endothelial nitric oxide (NO). Endothelial NO in the cerebral circulation is generated by endothelial nitric oxide synthase (eNOS) which under basal conditions is expressed exclusively in endothelial cells. Notably, cells of the brain parenchyma are no more than 15 µm away from a capillary suggesting endothelial NO may be an important signaling molecule between endothelial cells and microglia. Our hypothesis is that loss of bioavailable endothelial NO is a mechanistic link between cardiovascular risk factors and AD. We previously reported that eNOS knockout (-/-) mice had an altered microglial phenotype, including altered secretion of cytokines and aberrant protein expression. We sought to define the effects of reduced bioavailability of endothelial NO on microglial phenotype. Studies were performed on postnatally-derived microglia isolated from wild type and eNOS-/- pups. Most notably, we observed a significant increase in the expression of a disintegrin and metalloproteinase (ADAM) 17 in microglia derived from eNOS-/- mice ($P<0.05$; n=6). ADAM17 is the primary sheddase for triggering receptor expressed on myeloid cells (TREM)2. TREM2 is a critical regulator of microglial phenotype, including: proliferation, survival, phagocytosis, and cytokine production. Indeed, membrane bound TREM2 protein was significantly decreased in eNOS-/- microglia ($P<0.05$; n=3-4). Furthermore, cytosolic phospholipase (cPL) A2 and phosphorylated (p-) cPLA2 were significantly increased in eNOS-/-

microglia (P<0.05; n=3). Increased cPLA2 signaling suggests eNOS-/- microglia have increased mobilization of arachidonic acid (AA). AA can act as a signaling molecule as well as substrate for cyclooxygenase (COX) enzymes and production of eicosanoids which are important mediators of the inflammatory response. Lastly, we observed significant alterations in the secretion of the cytokines, tumor necrosis factor-α and interleukin-10 (P<0.05; n=4-5). Taken together, these data demonstrate that loss of endothelial NO leads to a dysfunctional phenotype in microglia. Our findings suggest endothelial NO-dependent modulation of microglial phenotype is an important mechanistic link between cardiovascular risk factors and the development of AD pathology.

Disclosures: S.A. Austin: None. **Z.S. Katusic:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.01

Topic: C.09.Stroke

Support: NIH 1R01NS104117 (NGB and LB)

Title: Robust neuroprotection by neuroprotectin D1, a docosahexaenoic acid-derived mediator, in experimental ischemic stroke

Authors: L. BELAYEV[1], A. OBENAUS[2], ***L. KHOUTOROVA**[3], P. MUKHERJEE[3], N. PETASIS[4], N. G. BAZAN[3];
[1]LSUHSC, New Orleans, LA; [2]Dept Pediatrics, Univ. California Irvine, Irvine, CA; [3]LSU, New Orleans, LA; [4]USC, Los Angeles, CA

Abstract: Stroke remains the fifth leading cause of death and of [MLA1] adult disability worldwide. Vascular occlusion followed by ischemic cascade triggers a pattern of cellular and molecular disturbances that include lipid peroxidation and neuronal injury. Neuroprotectin D1 (NPD1), a docosahexaenoic acid (DHA)-derived lipid mediator, downregulates apoptosis and, in turn, promotes cell survival. The purpose of this study was to investigate whether administration of synthetic NPD1 in either its sodium salt (SS) or as methyl ester (ME) is neuroprotective in model of focal cerebral ischemia. Male Sprague-Dawley rats were subjected to 2 h of middle cerebral artery occlusion (MCAo). As SS or ME, NPD1 (5µg/per rat) was dissolved in artificial CSF and administered into the right lateral ventricle at 3 h after onset of stroke. There were three groups: NPD1-SS, NPD1-ME and CSF (50µl). Neurological function was evaluated on days 1, 3, and 7 after MCAo. *Ex vivo* MRI and immunohistochemistry were conducted on day 7. All NPD1 treatments greatly improved neurological scores in a sustained fashion up to the 7-day survival period (by 35-45%) compared to vehicle group. Ischemic core and penumbra volumes

(computed from T2WI) were significantly reduced by NPD1-SS and NPD1-ME treatments (core: by 59 and 69%; penumbra: 71 and 67%) and total lesion volumes (by 66 and 67%, respectively) compared to CSF-treated group. NPD1-treated rats showed less infarction with an increased number of NeuN- and GFAP-positive cells as well as SMI-71-positive vessels in the cortex and less IgG staining in the cortex. NPD1-mediated protection was extensive in the frontal-parietal cortex (tissue was salvaged by 84-94%), subcortex (70-78%), and total infarct volume, correction for brain swelling was dramatically reduced in all ELV-treated groups by 78-88%. Conclusion: We have shown that the administration of NPD1 provides high-grade neurobehavioral recovery, decreases ischemic core and penumbra volumes, as well as attenuates cellular damage, blood vessel integrity, and BBB disruption. It is reasonable to propose that NPD1 might provide the basis for future therapeutic applications.

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Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.02

Topic: C.09.Stroke

Support: VA Grant I01RX001141-01A1

Title: Stroke co-morbidities potentiate complement-dependent neuroinflammation after stroke

Authors: *A. TOUTONJI[1], S. TOMLINSON[2], A. ALAWIEH[2], C. ATKINSON[1]; [2]Microbiology and Immunol., [1]Med. Univ. of South Carolina, Charleston, SC

Abstract: Introduction: Following stroke, complement-dependent neuroinflammation exacerbates secondary injury and worsens acute and chronic outcomes. We have shown that an injury site-targeted complement inhibitor (B4Crry), that targets specifically to the ischemic brain, inhibits complement activation leading to improved outcomes. Stroke comorbidities have been shown to promote a pro-inflammatory environment in the brain and systemically, and to exacerbate inflammatory responses after injury. Here, we investigate the impact of age and smoking on acute outcomes after stroke and assess whether increased complement activation contributes to the worsening outcomes with stroke comorbidities. **Methods:** Mouse brain endothelial cells (bEnd3) were exposed to hypoxia followed by reperfusion with serum derived from either cigarette smoke (CS)-exposed mice or naïve mice, and IgM and C3d deposition assessed. Adult (12 weeks) and aged (1 year) mice were subjected to 1h transient middle cerebral artery occlusion. Animals were exposed to CS for 3-6 months (5hr/day, 5days/week) by burning 3R4F cigarettes using a smoking machine. Animals were treated with B4Crry or vehicle

intravenously 2h post-MCAO. Survival analysis and neurological deficit scores were performed up to 7 days. Brains were extracted for histological and molecular analyses. **Results:** Following hypoxia, bEnd3 cells exposed to serum from CS-exposed mice had higher C3d and IgM deposition compared to naïve serum. Older and CS-exposed mice had significantly worse neurological deficits and mortality compared to younger adults post-MCAO. B4Crry reduced mortality and motor deficits in young, old and old+CS mice with a higher effect size in comorbid animals. Age and/or CS exposure resulted in larger infarct volumes, and increased levels of C3d deposition and microglial activation compared to young adults, but aged/CS animals treated with B4Crry fared comparable to young adults. **Conclusion:** The pro-inflammatory effects of aging and smoking contribute to worse stroke outcomes, and these effects can be successfully mitigated by injury site-targeted complement inhibition. <!--EndFragment-->

Disclosures: A. Toutonji: None. **S. Tomlinson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Admirx. **A. Alawieh:** None. **C. Atkinson:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.03

Topic: C.08. Ischemia

Support: NIH Grant AG049821
NIH Grant NS094834

Title: Recurrent hypoglycemia promotes cerebral microvascular mitochondrial dysfunction and enhanced ischemia-reperfusion injury to the brain

Authors: *W. R. EVANS[1,2], S. S. V. P. SAKAMURI[2], J. A. SPERLING[2], Q.-S. LE[1], V. N. SURE[2], D. W. BUSIJA[1,2], R. MOSTANY[1,2], P. V. G. KATAKAM[1,2];
[1]Tulane Brain Inst., Tulane Univ., New Orleans, LA; [2]Dept. of Pharmacol., Tulane Univ. Sch. of Med., New Orleans, LA

Abstract: Objective. Diabetes mellitus (DM) patients receiving blood glucose lowering medications risk the potential for recurrent hypoglycemia (HG) episodes. HG has been implicated in increased risk of morbidity and mortality associated with cardiovascular disease and increased susceptibility to ischemia-reperfusion (IR) injury such as a stroke or myocardial infarction. However, mechanistic data of how HG increases the damage done by IR injury is lacking. Our hypothesis is that HG exacerbates IR injury to the brain by impairing blood brain barrier (BBB) integrity driven by cerebral microvascular mitochondrial dysfunction.
Methods. Male C57Bl/6 mice aged 2-5 months were exposed to recurrent insulin-induced

hypoglycemia (RH; blood glucose level <70mg/dL) or recurrent saline control (RS) for 60 min/day for 5 days. One day after, mice were exposed to transient middle cerebral artery occlusion (tMCAO) for 30 minutes. Mice were given post-operative care and allowed to reperfuse for 48 hours. Infarct volumes were determined with TTC staining. A separate cohort of mice were exposed to either RH or RS after which they were euthanized and cerebral microvessels were freshly isolated for *ex vivo* mitochondrial respiration measurements using Seahorse XFe24 Analyzer (Agilent). BBB integrity was measured *in vivo* in a third group of mice using two-photon excitation microscopy of the brain vasculature by measuring extravasation of fluorescent dextrans.
Results. RH significantly increased tMCAO induced infarct volume (25.38 +/- 3.72% ipsilateral cortex volume vs 42.17 +/- 3.02%, p = 0.0057, N = 6). Measured as raw volume, RH lead to a mean infarct volume of 120.50 +/-10.11 mm^3 vs 70.82 +/- 12.21 mm^3 in the RS group (p = 0.0107). In our mitochondrial respiration experiments, microvessels exposed to RH had significantly decreased ATP production (1.108 +/- 0.052 vs. 0.3714 +/- 0.1859 OCR in pmoles/min/µgram protein, p = 0.0189, N = 3) and trended toward a decrease in basal respiration (4.048 +/- 0.1248 vs 3.227 +/- 0.2858 OCR. p = 0.058).
Conclusions. RH increases damage done by IR to the brain and impairs mitochondrial respiration in cerebral microvessels. Our work shows that RH is potentially a driving cause of long term promotion of cerebrovascular complications of DM, and that prevention of RH incidence should be an utmost priority in treatment.

Disclosures: W.R. Evans: None. **S.S.V.P. Sakamuri:** None. **J.A. Sperling:** None. **Q. Le:** None. **V.N. Sure:** None. **D.W. Busija:** None. **R. Mostany:** None. **P.V.G. Katakam:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.04

Topic: C.08. Ischemia

Title: The role of glutamate antiporter, system x_c-, in regulation of electrophysiological hypoxic responses in hippocampal slices

Authors: *B. S. HEIT[1], A. CHU[1], A. SANE[2], J. E. RICHMOND[4], D. E. FEATHERSTONE[3], A. RAY[2], J. R. LARSON[5];
[1]Psychiatry, [3]Biol. Sci., [2]Univ. of Illinois at Chicago, Chicago, IL; [4]Biolog Sci., Univ. Illinois Chicago, Chicago, IL; [5]Dept Psychiat, Univ. of Illinois at Chicago Dept. of Psychiatry, Chicago, IL

Abstract: Ischemic stroke remains the leading cause of adult-disability in developed and developing countries. Due to the unpredictability of ischemic events, the rapid neuronal death

that ensues, and the inefficacy of post-stroke rehabilitative efforts, the development of pre-ischemic interventions that reduce stroke severity are the most attractive. One particularly vulnerable area to ischemic trauma is the hippocampus, insomuch that with any non-specific blood loss to the brain, the CA1 neurons are the first to experience cell death. Importantly, much of the "ischemic cascade" can be reproduced by transient deprivation of O_2 to *in vitro* hippocampal slices. The cystine/glutamate antiporter, system x_c-, with specific subunit xCT, is identified as the primary source of extracellular glutamate in the brain. This glial membrane-bound transport system serves as a source of cystine, which is intracellularly converted to cysteine - the rate-limiting substrate for glutathione synthesis. The high rate of O_2 consumption in the brain renders this antiporter vital to antioxidant defense, and its expression is rapidly upregulated during oxidative stress. However, the release of glutamate into the extracellular space, accompanying the uptake of cystine, could alter the synaptic response during O_2 deprivation. We previously reported findings, which suggest that glutamate release via system x_c- exacerbates ischemic excitoxicity by shortening the latency of time to anoxic depolarization (AD). The current study further elucidates this phenomenon by comparing xCT-KO ($xCT^{-/-}$) mice with wild-type (WT) littermate control mice. Slices prepared from eight-week old mice were tested in a battery of electrophysiological measures. We first show that $xCT^{-/-}$mice exhibit no alteration in paired-pulse facilitation, suggesting their anoxia tolerance is not a function of presynaptic calcium release. Next, we provide evidence that system x_c- regulates hippocampal responses to anoxia via effects on extracellular glutamate levels. This was shown in experiments varying extracellular glutamate concentrations, pharmacological antagonism of glutamate receptors, and pharmacological antagonism of system x_c-. Finally, during hypoxic conditions ($30\%O_2/70\%N_2$), $xCT^{-/-}$mice display attenuated synaptic suppression, a faster return to baseline amplitudes upon reoxygenation, and post-hypoxic potentiation. Taken together, our findings confirm system x_c- as a regulator of ischemia tolerance, implicating the antiporter as an attractive target for the development of pharmacology for stroke neuroprotection.

Disclosures: **B.S. Heit:** None. **A. Chu:** None. **A. Sane:** None. **J.E. Richmond:** None. **D.E. Featherstone:** None. **A. Ray:** None. **J.R. Larson:** None.

Nanosymposium

540. Stroke II

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Presentation Number: 540.05

Topic: C.08. Ischemia

Support: NIH/ NS094859
AHA predoctoral fellowship-18PRE34020126

Title: Differential effects of young and old serum exosomes on ischemic stroke outcomes in aged rats

Authors: *H. ZHANG[1], K. JIN[2];
[1]Pharmacol. & Neurosci., Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX; [2]Univ. of North Hlth. Sci. Ctr., Fort Worth, TX

Abstract: Background: Aging is associated with striking increases in the incidences of stroke and neurodegenerative diseases, both of which are major causes of disability among those age 70 years and older in the United States. Despite progress in understanding molecular mechanisms of neuronal cell death after stroke, effective treatment remains elusive. Recent studies showed that systemic factors in the blood can profoundly reverse aging-related impairments, and our study show that aging systemic milieu could worse outcome after ischemic stroke in rats. However, the underlying mechanism remain unclear. Exosomes are extra-cellular microvesicles that play important roles in intercellular signaling and in regulating various physiological and pathological conditions. Here, we explore the role of young and old serum-derived exosomes on ischemic outcome in aged rats. **Method:** The exosomes were isolated from serum of young or old rats, and then were intravenously injected into aged ischemic rats via tail for 3 days, respectively. Infarct volume was determined with triphenyltetrazolium chloride (TTC) staining and motor function was assessed with neurobehavioral tests including running ladder and cylinder tests. To elucidate the potential mechanism underlying the functional improvement or deterioration, neuroplasticity was examined after treatment of young and old serum exosomes using Golgi-Cox staining and data were analyzed using Imaris software. **Results:** We found that injection of young serum exosomes into aged ischemic rats reduced infarct volume and improved motor functional deficits. On the contrary, injection of old serum exosomes increased infarct volume and worsened motor function. We also found that the dendritic length and spine numbers were significantly increased after injection of young exosomes, while decreased after injection of old exosomes. **Conclusion:** Our data suggest that young and old serum exosomes differentially affect functional outcome in aged rats after ischemic stroke, which potentially be translated into novel therapeutic intervention by minimizing the destructive potential of detrimental molecules and enhancing the beneficial contributions to repair the damaged brain.

Disclosures: H. Zhang: None. **K. Jin:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.06

Topic: C.08. Ischemia

Support: Florida Department of Heath#7JK01 funds

Title: Post-stroke whole body vibration reduces systemic innate immune inflammation in nicotine exposed reproductively senescent rats

Authors: *N. A. K. KERR[1], W. J. MORENO[1], J. SANCHEZ[1], O. E. FURONES-ALONSO[1], W. DIETRICH, III[4], A. P. RAVAL[2], H. M. BRAMLETT[3];
[2]Neurol., [3]Dept Neurosurg., [1]Univ. of Miami, Miami, FL; [4]Neurol Surgery, Univ. of Miami Sch. of Med., Miami, FL

Abstract: Cigarette smoking is a risk factor for stroke, which is a leading cause of death and disability worldwide. Stroke kills more women than men and the underlying mechanisms responsible for higher incidence and severity of stroke in women remain unknown. Nicotine addiction causes unique detrimental effects on women's brains and nicotine has been proven to enhance pro-inflammatory cytokines. The role of inflammatory cytokines in stroke pathogenesis has been widely studied, however there is a lack of treatment strategies targeting the inflammatory mechanisms post-stroke. Whole Body Vibration (WBV) has shown promise as a novel rehabilitative strategy for chronic disabilities seen post-stroke (Raval et al., 2018). Our previous work showed that reproductively senescent female rats exposed to transient middle cerebral artery occlusion (tMCAO) showed reduction in innate inflammatory proteins, including IL-1β as well as an increase in brain-derived neurotrophic factor (BDNF) after 30 days WBV treatment. The goal of this study is to determine whether WBV treatment plays a role in the anti-inflammatory mechanisms involved in post-stroke recovery. Nicotine or saline exposed adult female rats underwent tMCAO; 90 min/ sham-surgery and randomly assigned (n = 6-8 per group) to either WBV or control groups. Animals placed in the WBV (40 Hz) group underwent 30 days of WBV treatment performed twice daily for 15 min each session for 5 days each week. Animals were sacrificed after 30 days of WBV treatment and blood samples were collected to cytokine and growth factors analysis using a Bioplex Assay. Bioplex assay we used included total of 27 targets, which included pro- and anti-inflammatory and growth factors protein. Results showed a decrease in expression of systemically circulating pro-inflammatory cytokines IL-2, IL-6, and IL-4 ($p<0.05$) in nicotine exposed tMCAO female rats that underwent WBV treatment compared to saline exposed tMCAO female rats. These cytokines are important to regulation of the innate and adaptive immune response seen post-stroke. The study of circulating proteins shows promise for determining biomarkers for chronic stroke complications. Lastly, targeting these cytokines using WBV treatment may have beneficial effects for female smokers in the delayed inflammatory response seen post-stroke.
Reference:
Raval AP, Schatz M, Bhattacharya P, d'Adesky N, Rundek T, Dietrich WD, Bramlett HM (2018) Whole Body Vibration Therapy after Ischemia Reduces Brain Damage in Reproductively Senescent Female Rats. Int J Mol Sci 19.
* APR and HMB are corresponding authors

Disclosures: **N.A.K. Kerr:** None. **W.J. Moreno:** None. **J. Sanchez:** None. **O.E. Furones-Alonso:** None. **W. Dietrich:** None. **A.P. Raval:** None. **H.M. Bramlett:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.07

Topic: C.08. Ischemia

Support: Endowment from Chantal Scheinberg and Peritz Scheinberg (APR)
Florida Department of Health #7JK01 funds (APR)
American Heart Association Grant-in-aid #16GRNT31300011 (APR)

Title: Post-stroke physical exercise reduces ischemic brain damage and improves cognition in reproductively senescent female rats

Authors: *S. SARAVANAN[1], C. FURONES[1], W. ZHAO[2], K. DAVE[1], M. A. PEREZ-PINZON[1], A. P. RAVAL[1];
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Abstract: Stroke disproportionately kills more women than men and even a mild stroke causes disability in post-menopausal women. Menopause is defined as the menstrual cycle ceases due to anovulation. Notably, menopause is not an abrupt event. The overall process of menopause lasts for years and during that period, disruption of multiple estrogen-regulated systems and domains of cognitive function can be affected. Cognitive decline is a significant consequence of stroke survivors and two-thirds of stroke survivors experience cognitive deficits that last at least up to 6 years post-stroke. Our earlier study demonstrated that physical exercise (PE) reduced post-stroke brain injury and improved cognitive functions in male rats. However, efficacy of PE in female counterparts remains elusive and the focus of our current study is to evaluate the improvement of post-stroke cognitive function in female rats. Reproductively senescent Sprague–Dawley female rats were exposed to transient middle cerebral artery occlusion (tMCAO; 90 min) and randomly assigned to either PE or sham-PE groups. After three to five days, rats underwent sham-PE (0m/min speed) or PE (15m/min speed) for 30 mins either every day or alternate day for five times on treadmill. The rats that underwent alternate day paradigm were treated with ER-β agonist (beta 2, 3-bis(4-hydroxyphenyl) propionitrile; DPN; 1mg/kg) or vehicle-DMSO immediately following PE/sham-PE session to determine the synergistic effect with physical exercise since ER-βagonist is shown to reduce ischemic damage. Seven days after the last PE/sham-PE, rats were tested for hippocampal-dependent contextual fear conditioning and freeze time was measured. Following behavioral testing, rats' brains were processed for histology and infarcted area was measured using MCID software. Results demonstrated that post-tMCAO continuous PE did not reduce ischemic damage. However, alternate PE regimen with or without ER-β agonist reduced infract volume by 20% and 23%, respectively. Similarly, alternate PE regimen showed increased freezing on the second day of fear conditioning by 15%, indicating improved spatial memory. Overall, the study suggests that an alternate day PE paradigm and ER-

β activation improves post-stroke cognition and future studies delineating underlying mechanism could help identify therapies to prevent/reduce stroke related cognitive decline in menopausal women stroke patients.

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Nanosymposium

540. Stroke II

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Presentation Number: 540.08

Topic: C.08. Ischemia

Support: National Natural Science Foundation of China 31540020, 31671048
The Free Exploration Foundation of Shenzhen Science and Technology Innovation Committee JCYJ20160530192506314
The Provincial Natural Science Foundation of Hunan Province 2017JJ2041

Title: Identification of protective role of enolase1 in cerebral ischemia-induced neuronal injury and of potential ischemia biomarker by brain slice-based SELEX

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Abstract: Stroke is one of leading causes of disability and death among adults worldwide, and results in numerous biochemical alterations. While the mechanisms underlying neuronal death and dysfunction remain poorly understood. We investigated the differential proteomic profiles of mouse brain homogenate with 3 h of middle cerebral artery occlusion (MCAO) ischemia, or sham, by mass spectrometry. We identified Enolase1 (ENO1), a key glycolytic enzyme, as a potential mediator of neuronal injury in MCAO ischemic model. Immunohistochemical analysis revealed that ENO1 is localized in neuronal cytoplasm and dendrites. Interestingly, the expression level of ENO1 was significantly increased in the early stage, but dramatically decreased in the late stage, of cerebral ischemia *in vivo*, and of cultured hippocampal neurons treated with oxygen/glucose deprivation (OGD) *in vitro*. Strikingly, ENO1 overexpression in cultured neurons alleviated dendritic and spinal loss caused by OGD treatment. The neuronal injury caused by OGD treatment *in vitro* or ischemia *in vivo* was mitigated by the application of PEP. Taken together, these data revealed that ENO1 plays a novel and protective role in cerebral

ischemia-induced neuronal injury, highlighting a potential of ENO1 as a therapeutic target of neuronal protection from cerebral ischemia. Moreover, we also utilized frozen brain slices of middle cerebral artery occlusion (MCAO) in a mouse model of ischemia to select a specific binding aptamer, termed LCW17, by tissue-based SELEX. We identified the binding target of LCW17 as Vigilin. Vigilin is increased in ischemia brain slices and exhibits enhanced release from cultured hippocampal neurons after oxygen glucose deprivation *in vitro*. In summary, Aptamer LCW17 and Vigilin, may potentially be applied to define the molecular mechanism underlying ischemic stroke, as well as its diagnosis.

Disclosures: H. Tu: None. **W. Jiang:** None. **C. Liu:** None. **X. Tian:** None. **P. Yang:** None. **W. Tan:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.09

Topic: C.08. Ischemia

Support: Florida Department of Heath#7JK01

Title: Chronic nicotine exposure hinders whole body vibration therapy induced ischemic protection in the brain of reproductively senescent female rats

Authors: *A. P. RAVAL[1], W. MORENO[2], J. SANCHEZ[2], N. KERR[2], O. E. FURONES-ALONSO[2], W. DIETRICH, III[2], H. M. BRAMLETT[2,3];
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Abstract: Stroke disproportionately kills more women than men and the risk of stroke remains high even at a young age among women smokers. Smoking prior to stroke is associated with increased post-stroke frailty. Frailty is characterized by an increased vulnerability to acute stressors and the reduced capacity of various bodily systems due to age-associated physiological deterioration. Such age related physiological deterioration of bone in laboratory animals and humans has shown to reverse after therapeutic intervention of whole body vibration (WBV) (*1*). Our recently published study shows that post-stroke WBV intervention reduces ischemic brain damage in reproductively senescent female rats (*2*), suggesting WBV may be a potential therapy to reduce post-ischemic frailty and improve functional and cognitive outcomes after stroke. In the current study we aim to test the efficacy of WBV in reducing post-ischemic frailty and improving physical activity and cognition using a rat model of smoking attributed nicotine. Nicotine or saline exposed adult female rats underwent transient middle cerebral artery occlusion

(tMCAO; 90 min) / sham-surgery and randomly assigned (n = 6-8 per group) to either WBV or control groups. Animals placed in the WBV (40 Hz) group underwent 30 days of WBV treatment performed twice daily for 15 min each session for 5 days each week. We monitored the frailty index (FI) prior to and 1 month after tMCAO alone or in combination with WBV. The FI was composed of the following criteria: 1) activity levels, 2) blood pressure (BP), 3) basic metabolic status, and 4) cognitive performance of rats. Animals were sacrificed on the 30th day of WBV treatment, and brain tissue was harvested for histopathological analysis. Post-tMCAO WBV did not change activity levels or BP in nicotine or saline treated rats. Post-tMCAO WBV cognitive performance improved in saline group as compared to nicotine exposed rats. Sensorimotor function was also improved in tMCAO WBV saline group compared to nicotine-exposed rats. We observed 56% reduction in infarct volume of WBV treated rats as compared to control ($p < 0.05$). This difference was not seen in nicotine treated groups. The post-ischemic WBV intervention had no detrimental effects on the frailty parameters, decreased brain damage, and reduced frailty in control female rats, but not in the nicotine-exposed group. This suggests that WBV may be a potential therapy for non-smokers to reduce post-ischemic frailty and improve functional and cognitive outcomes after stroke.

Reference:
1. H. M. Bramlett *et al.*, *Osteoporosis international* **25**, 2209-2219 (2014).
2. A. P. Raval *et al.*, *Int J Mol Sci* **19**, (2018).

Disclosures: **A.P. Raval:** None. **W. Moreno:** None. **J. Sanchez:** None. **N. Kerr:** None. **O.E. Furones-Alonso:** None. **W. Dietrich:** None. **H.M. Bramlett:** None.

Nanosymposium

540. Stroke II

Location: Room S505

Time: Tuesday, October 22, 2019, 1:00 PM - 3:30 PM

Presentation Number: 540.10

Topic: C.08. Ischemia

Support: American Heart Association Grant #16GRNT31300011

Title: Nicotine alters brain energy metabolism and exacerbates ischemic injury in female rats

Authors: *S. PATEL[1], F. DIAZ[2], A. P. RAVAL[1];
[1]Peritz Scheinberg Cerebral Vascular Dis. Res. Laboratory, Dept. of Neurol., Univ. of Miami, Miami, FL; [2]Leonard M. Miller Sch. of Med., Miami, FL

Abstract: Smoking-derived nicotine (N) and oral contraceptives (OC) synergistically exacerbates ischemic brain damage and alters mitochondrial function in female. Our studies show that N toxicity is exacerbated by OC via altered mitochondrial function, which involves a defect in the activity of cytochrome c oxidase, the terminal enzyme of the ETC. Here, we

investigated the global metabolomic profile of brains of adolescent and adult female rats exposed to N+/-OC. We also determined if pharmacological stimulation of mitochondrial biogenesis (using bezafibrate- clinically approved treatment of hyperlipidemias) abrogates N+OC-induced mitochondrial dysfunction in brain. Adolescent (6 weeks old) and adult (12 weeks old) Sprague-Dawley female rats were randomly (n = 8/group) exposed to either saline, N (4.5 mg/kg) +/- OC for 16-21 days. At the end of the treatment, brain tissue was harvested to obtain an unbiased global metabolomic profile (performed by Metabolon Inc.) The metabolomic study was complemented with western blot analysis and enzyme activity measurements of key altered pathways. To determine the effects of bezafibrate along with N+OC on mitochondrial biogenesis, adolescent and adult rats exposed to N+/-OC were fed *ad libitum* with either standard chow or 0.15% (w/w) bezafibrate-supplemented chow. Mitochondrial biogenesis was assessed by determining the mtDNA levels compared to nuclear DNA using real time PCR, by western blots of oxidative phosphorylation system subunits and by enzymatic determination of complex IV activity and citrate synthase. Pathway enrichment analysis showed significant changes in energy metabolism (glycolysis and TCA cycle) and neurotransmitters in both adolescent and adult rats exposed to N+/-OC in relation to saline treatment. The changes were more pronounced in adolescent rats with a significant decrease in glucose, glucose 6-phosphate and fructose-6-phosphate, along with a significant increase in pyruvate in N and N+OC exposed groups when compared to saline ($p<0.05$), suggesting alterations in the glycolytic pathway. In addition, there were significant differences on neuropeptides such as GABA. Western blot analyses of glycolytic enzymes support the observed metabolic changes. Nicotine and N+OC exposure increased brain glycolysis in an age-dependent manner. Since glucose metabolism is critical for brain physiology, altered glycolysis deteriorates neural function, thus exacerbating ischemic brain damage. Discerning the exact effects of N+/-OC on overall brain metabolism and the molecular mechanisms affecting mitochondrial function at different ages will open a new window for future therapeutic intervention.

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Nanosymposium

541. Traumatic Brain Injury

Location: Room S404

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 541.01

Topic: C.10. Brain Injury and Trauma

Support: R01NS092847
P41EB002520

Title: 3D *in vitro* brain tissue model to identify mechanisms of traumatic brain injuries

Authors: *V. LIAUDANSKAYA[1], J. Y. CHUNG[2], N. ROULEAU[1], A. N. BERK[1], C. MIZZONI[1], I. GEORGAKOUDI[1], M. J. WHALEN[2], T. J. F. NIELAND[1], D. L. KAPLAN[1]; [1]Tufts Univ., Medford, MA; [2]Pediatrics, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Several types of traumatic brain injuries (TBIs) are recognized, such as concussion, contusion, hemorrhage and blast. The molecular mechanisms that are activated upon injury are poorly understood, making TBI diagnosis and treatment challenging. *In vivo* experiments on rodents are the predominant model for TBI research. However recently, engineered 3D tissue models have emerged as a powerful resource to study brain biology and pathology due to their simplicity, relevance and tunable features. We describe an *in vitro* 3D brain-like tissue model for traumatic brain injury, and use this system to characterize early cell-molecular events in response to contusion injury. Correlating the outcomes from the 3D tissue model subjected to controlled cortical impact (CCI) to results from our analogous *in vivo* animal injury model was instrumental in validating the bioengineered brain-like tissue as relevant for TBI. The 3D *in vitro* brain tissue model consists of mouse embryonic cortical neurons grown on a silk protein porous ring mimicking the grey (neuronal soma) matter, and a core inner window mimicking the white matter (neurites) of the cortex. The *in vitro* 3D brain tissue, embedded in collagen hydrogel, formed dense networks of neurons expressing Tuj1 and MAP2 neurite markers and Synapsin-1, Psd95 and Gephyrin positive excitatory and inhibitory synapses, and small amounts of astrocytes and microglia. Critically, time course analysis identified structural damage within minutes after CCI impact, initially in the direct impact area that subsequently propagated throughout the entire 3D brain tissue. The immediate degradation of the neural network was followed by a delayed onset of neural death, based on LDH release and TUNEL confocal immunofluorescence imaging, and a gradual release of glutamate. Analysis of phosphorylated MLKL (mixed lineage kinase domain like pseudokinase) suggests the involvement of the necroptotic pathway in the 3D brain-like tissue, akin to rodents exposed to CCI. Furthermore, we show the deactivation of the Akt/mTOR signaling pathway, a key cellular regulator of cellular homeostasis in both *in vitro* and *in vivo* CCI systems. In summary, this new *in vitro* 3D brain tissue model mimics several important aspects of the *in vivo* neuronal response to trauma, providing evidence of the utility of our bioengineering approach to study functional, structural and molecular changes over time after injury. Moreover, our system can be used to assess possible prophylactic treatments and post injury interventions. We thank the NIH (R01NS092847, P41EB002520) for support.

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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.02

Topic: C.10. Brain Injury and Trauma

Support: NIH R21 NS103088
NIH R01 NS50465

Title: Spatial and temporal single cell molecular dissection of traumatic brain injury

Authors: *D. ARNESON[1,2], G. ZHANG[1], R. FOREMAN[1], I. AHN[1], G. DIAMANTE[1], Z. YING[1], Z. HEMMINGER[1], R. WOLLMAN[1], F. GOMEZ-PINILLA[1,3,4], X. YANG[1,2,5,6]; [1]Dept. of Integrative Biol. and Physiol., [2]Bioinformatics Interdepartmental Program, [3]Dept. of Neurosurg., [4]Brain Injury Res. Ctr., [5]Inst. for Quantitative and Computat. Biosci., [6]Mol. Biol. Inst., UCLA, Los Angeles, CA

Abstract: The complex neuropathology of traumatic brain injury (TBI) is difficult to dissect, given the cellular heterogeneity of affected brain regions. Dysfunction during TBI results in cognitive decline that may escalate to other neurological disorders, the molecular basis of which is hidden in the genomic programs of individual cells. This complexity is further exacerbated by disrupted circuits within and between tissues which occur at different timescales and in spatial domains. We profiled three tissues (hippocampus, frontal cortex, and blood leukocytes) at the acute (24hr) and chronic (7days) phases of mild TBI at single cell resolution and demonstrate that the molecular and cellular circuitry within and between tissues are rewired by TBI at different timescales. We also applied MERFISH, a high throughput image-based single cell transcriptomic technology that offer single molecule quantification, to localize the spatial domains and specific cell populations involved in our network models. Our results offer a systems-level understanding of the dynamic and spatial regulation of gene programs by TBI and pinpoint key target genes, pathways, and cell circuits that are amenable to therapeutics.

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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.03

Topic: C.10. Brain Injury and Trauma

Support: VA Rehabilitation Research & Development, Merit Review B77421 “Mild TBI and Biomarkers of Neurodegeneration”

Title: Individualized assessment of longitudinal alterations after repetitive mild blast injury in Veterans using FDG-PET

Authors: *D. J. CROSS[1], S. MINOSHIMA[1], G. E. TERRY[2], D. G. COOK[2], J. S. MEABON[2], K. PAGULAYAN[2], M. RASKIND[2], E. PESKIND[2];
[1]Univ. of Utah, Salt Lake City, UT; [2]VA Puget Sound, Seattle, WA

Abstract: Repetitive mild traumatic blast injury (rmTBI) may lead to an increased risk of neurodegeneration. The goal of this study is to assess longitudinal alterations in the metabolic activity in Veterans with previous rmTBIs using Positron emission tomography with [^{18}F]-fluorodeoxyglucose (FDG-PET). Methods: Ten Veterans with rmTBI (age 38.0±10.8, range 25-59 yrs) and 4 deployed controls (DC) with no blast exposure (age 35.8±7.7, range 28-45 yrs) received 2 FDG-PET scans (interval 3.3±0.8 and 3.0±0.29 yrs for DC and mTBI, respectively: t[12]=0.44, n.s.). Community controls (n=9, 28.0±8.1, range 20-45 yrs) were used as reference normal data. Images were anatomically standardized, normalized to global and Z-score maps of hypometabolic pixels (HPs) were created by comparing to the normal database. A custom algorithm counted the number of HPs in 26 brain regions with Z>1.64 on individual Z-maps for each paired image set. Longitudinal changes in number of HPs for each region, total global (GBL), and cortex (CTX) were counted and group differences assessed statistically. To overcome challenges from heterogeneous brain reorganization and injury patterns, we calculated a ratio of the number of regions (RR) with decreased HPs divided by the number of regions indicating increased HPs as a general assessment of decline (<1.0) or recovery (>1.0). Results: Group-wise comparisons between rmTBI and DC of scan 1, scan 2, and scan 2-1 differences showed scattered regional decreases in rmTBI that did not achieve statistical significance after correction for multiple comparisons. No between or within group differences were found among GBL or CTX regions, indicating that variability of individualized longitudinal changes obscured group differences. One of 4 DCs had RR<1.0 (RR=0.64) (25%) indicating increases in HPs and 3 DCs RR>1.0 (range 1.67 - 2.75) indicated improvement (DC RR=1.42±0.86, mn+sd). In rmTBIs, 8/10 subjects (80%) had RR<1.0 (range 0.26-0.75) indicating decline (increased HPs) and 2 subjects RR>1.0 indicating FDG-PET improvement (RR=7 and 1.67 respectively, rmTBI group RR=0.74±2.03). Chi-square analysis indicated a significant difference between the number of subjects declining in rmTBI versus DC ($p \leq 0.05$). Although group-wise longitudinal changes were not found, a ratio of regions showing reduced versus increased HPs was able to differentiate individuals that may be declining from those recovering after rmTBI. These results indicate that group-wise assessment of longitudinal imaging may not detect individualized changes after rmTBI. It is important for future therapeutic development to identify patients that may benefit from specific interventions.

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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.04

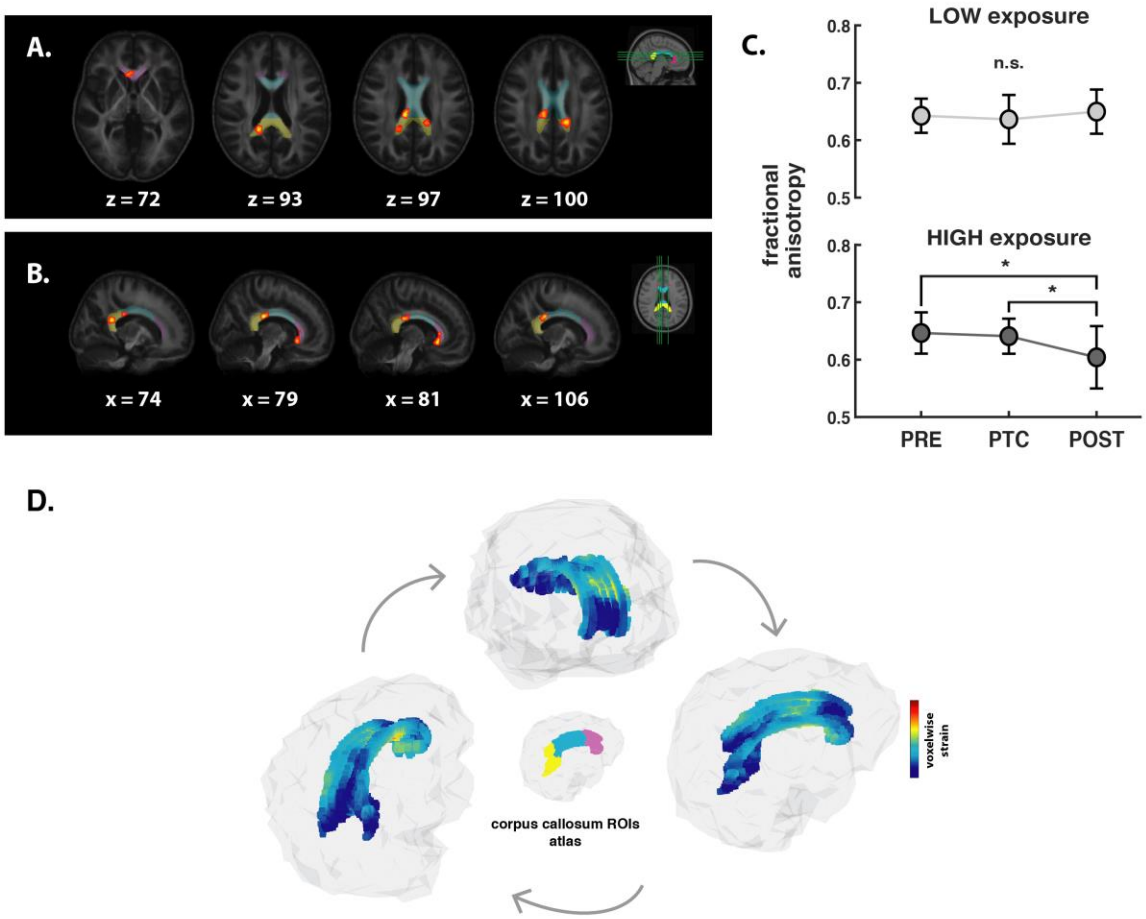
Topic: C.10. Brain Injury and Trauma

Support: Southeastern Ontario Academic Medical Organization (SEAMO)
Ontario Graduate Scholarship (OGS)
University of Auckland FDRF strategic initiative fund
Globalink Research Award (GRA) from Mitacs

Title: Novel strain-based analysis of tissue mechanics informs about changes in structural integrity within the corpus callosum following exposure to sub-concussive impacts

Authors: *A. A. CHAMPAGNE[1], E. PEPONOULAS[1], I. TEREM[3], A. ROSS[4], M. TAYEBI[5], Y. CHEN[1], N. S. COVERDALE[1], P. M. F. NIELSEN[6], A. WANG[5], V. SHIM[5], S. HOLDSWORTH[7], D. J. COOK[2];
[2]Neurosurg., [1]Queen's Univ., Kingston, ON, Canada; [3]Dept. of Electrical Engin., Stanford, CA; [4]N/A, N/A, ON, Canada; [5]Auckland bioengineering Inst., Auckland, New Zealand; [6]Auckland Bioengineering Inst. and Dept. of Engin. Sci., [7]Dept. of Anat. and Med. Imaging & Ctr. for Brain Res., The Univ. of Auckland, Auckland, New Zealand

Abstract: Increasing evidence for the cumulative effects of head trauma on structural integrity of the brain has emphasized the need to understand the relationship between tissue mechanic properties and injury susceptibility. Here, diffusion tensor imaging (DTI), helmet accelerometers and amplified magnetic resonance imaging (aMRI) were combined to gather insight about the region-specific vulnerability of the corpus callosum (CC) to microstructural changes in white-matter integrity upon exposure to sub-concussive impacts. Longitudinal decreases in fractional anisotropy were characterized in anterior and posterior regions of the for athletes sustaining more impacts to the head on a daily basis (**Figure 1A-C**). Using these findings as a basis for investigation, a novel strain analysis of sub-voxel motion based on the biomechanical response of brain tissues to cardiac impulseswas developed to show that differences in maximum strain (and thus possibly stiffness) along the tract (**Figure 1D**) may reveal a possible signature relationship between changes in white-matter integrity and tissue mechanical properties. In light of these findings, additional information about the viscoelastic behavior of WM tissues upon exposure to external forces may be imperative in elucidating the mechanisms responsible for region-specific differences in injury susceptibility observed, for instance, through changes in micro-structural integrity following exposure to sub-concussive collisions.
Figure 1.(A-B) Four significant clusters are overlaid over the group-mean fractional anisotropy (FA) map, along with the segmented corpus callosum (pink = genu, blue = body, yellow = splenium), to show the spatial distribution of the white-matter changes along the tract. (C) Mean FA (±standard deviation) extracted for the entire significant region-of-interest showing that changes in micro-structural integrity were specific to players who sustained a greater number of impacts per session (HIGH group). (D) The group-based averaged principal maximum strain masked for the corpus callosum.



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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.05

Topic: C.10. Brain Injury and Trauma

Support: OUHSC Summer Undergraduate Research Program
OU College of Pharmacy Seed Grant
AACP New Investigator Award
Oklahoma NSF EPSCoR Award

Title: Temporal changes in cerebrospinal histamine correlate with neurobehavioral deficits following mild traumatic brain injury in rats

Authors: *M. P. BAIER[1], A. C. EDWARDS[1], C. W. MOEHLENBROCK[1], E. F. FALCON[1], M. R. LERNER[2], H. O. AWWAD[1,3];
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Abstract: Histamine is an inflammatory mediator released by mast cells in the body and functions as a neurotransmitter in the central nervous system. In non-TBI models, histamine and histamine receptors have been shown to modulate memory loss and long-term pain. Altogether, this makes histamine a potential biomarker for TBI-related consequences. The goal of this study was to quantify histamine levels in biological fluids and to correlate these changes with injury markers and neurobehavioral deficits following a mild TBI (mTBI) in adult male Sprague Dawley rats. Neurobehavioral deficits and pain sensitivity were assessed in the first 2 weeks post-injury using rotarod, elevated plus maze, acquisition learning memory, tactile allodynia and thermal hyperalgesia. Cerebrospinal fluid (CSF), plasma, and brain samples were collected from rats euthanized on days 1, 8 or 16 post-injury or sham surgery. Histamine concentration measured by enzyme-linked immunosorbent assays in CSF of mTBI rats (58.5 ± 10.8 nM) was two-fold higher than CSF of naïve (24.7 ± 4.2 nM) and sham (27.2 ± 3.1 nM) rats collected at day 1 post-TBI ($p<0.05$; one-way ANOVA with Tukey's posthoc test, n=3-6). Plasma histamine concentrations were similar among sham and mTBI rats. Immunoblotting analysis of injury (Glial fibrillary acidic protein, Tau) and mast cell (tryptase) markers showed a transient increase in CSF collected on day 1 post-injury compared to non-injured rats, which returned to normal by day 16 post-injury. Mast cell degranulation was observed only in ipsilateral brain regions of day 1 mTBI rats compared to contralateral regions using immunohistochemistry. Increases in histamine, tryptase and injury markers on day 1 correlated with mTBI-induced deficits in rotarod performance and increased pain sensitivity on the same day and following days up to day 8 post-injury. mTBI-induced neurobehavioral deficits showed substantial recovery by day 15 post-injury. In conclusion, mTBI induced an increase in histamine and tryptase levels in CSF 24 hours post-injury that correlates with the onset of neurobehavioral deficits. Our data suggests that histamine plays an early role in TBI pathology and may be a potential biomarker for TBI prognosis and recovery.

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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.06

Topic: C.10. Brain Injury and Trauma

Support: TRAIL-Labex
Fondation des "Gueules Cassées"
Eranet Neuron CNS-aflame

Title: Early neurovascular dysfunction is associated with long-term behavioural impairments after juvenile traumatic brain injury

Authors: *A. ICHKOVA[1], B. RODRIGUEZ-GRANDE[1], M.-L. FOURNIER[1], J. AUSSUDRE[1], E. ZUB[2], P. SICARD[2], N. MARCHI[2], J. BADAUT[1];
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Abstract: Vascular dysfunction is a hallmark of pediatric traumatic brain injury (TBI) and predicts poor outcome on the long term. We hypothesized that early changes in cerebral blood flow and vascular reactivity of the intraparenchymal blood vessels are associated with long-term behavioral dysfunction after juvenile mild TBI (jmTBI). We used a model of **C**losed **H**ead **I**njury with **L**ongterm **D**isorders (CHILD) where an electromagnetic impactor induces injury in postnatal day 17 C57BL6 mice. Cerebral perfusion was measured at 4h, 3, 7 and 30 days after jmTBI. Vascular reactivity to a thromboxane A2 receptor agonist (vasoconstrictor) and N-Methyl-D-Aspartate (vasodilator) was assessed in cortical acute slices at 1, 3, 7 and 30 days. Morphological analysis of the vessels and neuronal loss were assesed with histology and smooth muscle actin (α-SMA) expression was determined by Western blot. Long-term neurophysiological sequelae were evaluated with a behavioural tests battery and cortical electroencephalography. Hypoperfusion occurred at 4 hours post-injury with a return to control levels at day 7. The intraparenchymal blood vessels exhibited decreased diameters in jmTBI group at 1 day, but greater diameters at 7 days. Functional assessment of these vessels showed impairments with increased constriction and decreased dilation at day 1, and then decreased constriction but increased dilation at day 3 post-jmTBI. Interestingly, these vascular reactivity changes were not associated with alteration in α-SMA expression. Despite no neuronal loss, jmTBI mice exhibited anxious behaviour at all timepoints post injury associated with a signature of low gamma and high theta cortical EEG waves at 30 days. In summary, regional perfusion changes and changes in neurovascular coupling preceeded neuronal dysfunction and could contribute to the long-term EEG-behavioral modifications after jmTBI.

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Nanosymposium

541. Traumatic Brain Injury

Location: Room S404

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 541.07

Topic: C.10. Brain Injury and Trauma

Support: NJIT Startup funding

Title: Vascular pathology mediated traumatic brain injury and the regenerative treatment using peptide hydrogel

Authors: *X. MA, B. SARKAR, P. IGLESIAS-MONTORO, Z. SIDDIQUI, V. KUMAR, J. HAORAH;
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Abstract: Introduction: Traumatic brain injury (TBI) is a major health problem for over 3.17 million people in the USA. Hemorrhage and coagulation caused by vascular disruption after TBI is a severe issue in the emergency room for patients to recover. The objective of this project is to understand the mechanisms of brain injury and to facilitate regenerative medicines for the reversal of brain injury. We propose a regenerative methodology focusing on the provision of an angiogenic peptide to facilitate vascular growth at the brain injury site. From our previous publication, we have established an injectable self-assembling peptide-based hydrogel (**SLanc**) to generate a regenerative microenvironment for neovascularization at the injury site. The injectable drug delivery system provides sustained *in vivo* efficacy, and incorporates an angiogenic VEGF (vascular endothelial growth factor) mimic.
Materials and Methods: The angiogenic peptide SLanc contains a central self-assembling domain, an enzymatic cleavage site, and a VEGF-mimic moiety. The peptide is overall positively charged and soluble in aqueous, addition of counterions such as phosphate screens the repulsive interaction and leads to fibrillar self-assembly into a thixotropic hydrogel. Angiogenic effect of SLanc was examined in vivo in a lateral fluid percussion injury (FPI) model (8-week-old male Sprague Dawley rats). SLanc hydrogel was injected right after FPI into the injury site on the cortex. Controls included sham and injury with PBS injection (n=10 for each group). Vascular regeneration was evaluated at day 7 and day 14 post-TBI, by histologic staining, immunostaining, and Western Blot.
Results and Discussion: In this study, a moderate blunt injury model was used to cause physical vascular damage and hemorrhage. SLanc was then applied in injured rat brain for investigation of sustained release and angiogenesis. At day7 post-TBI, more blood vessels were observed than the control group, as well as activation of VEGF-receptor 2, demonstrating the angiogenesis was initiated by SLanc treatment. Moreover, the vascular marker alpha-smooth muscle actin and endothelial marker von-Willebrand factor (vWF) showed an increased blood vessels number.
Conclusions: Vascular pathology plays an important role in the underlying mechanisms of TBI, thus the angiogenic peptide was applied to repair the damaged vascular. Increased expression of VEGF-Receptor 2, endothelial cells and smooth muscle actin comparing with injury control indicated the activation of angiogenesis after SLanc treatment. The self-assembling peptide hydrogel SLanc nanofibers are angiogenic and promote vascular growth in the injured brain.

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Nanosymposium

541. Traumatic Brain Injury

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Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 541.08

Topic: C.10. Brain Injury and Trauma

Support: NIH R01NS50465

Title: Gut feelings in the traumatic brain injury pathogenesis

Authors: *F. GOMEZ-PINILLA[1,2], S. REGE[1], G. ZHANG[1], L. F. ROYES[3];
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Abstract: Clinical evidence indicates that TBI has profound effects on peripheral metabolism, however, underlying mechanisms are poorly understood. TBI research has primarily focused on the CNS, and little is known about the peripheral alterations that may compromise brain metabolic homeostasis, inflammation and exacerbate the pathophysiology of TBI. Rats were exposed to the effects of fructose in the drinking water (15% w/v, 3wks) before moderate fluid percussion injury (FPI). We found that TBI affected glucose metabolism, and signaling proteins for insulin and growth hormone in the liver; these effects were exacerbated by fructose ingestion. Fructose, principally metabolized in liver, potentiated the action of TBI on hepatic lipid droplet accumulation. Studies in isolated cultured hepatocytes identified growth hormone and fructose as factors for the synthesis of lipids. The liver has a major role in the synthesis of lipids used for brain function and repair. TBI and fructose also promoted alterations in genes that control peripheral metabolism in the hypothalamus suggesting that the hypothalamus can have a pivotal role for the actions of TBI and fructose on brain and body. Fructose-fed TBI animals had elevated levels of markers of inflammation, lipid peroxidation, and cell energy metabolism, suggesting the pro-inflammatory impact of TBI and fructose in the liver. In addition, TBI affected the microbe composition in the gut that could contribute to systemic and central pathology. The hypothalamic-pituitary-growth axis seems to play a major role on the regulation of the peripheral TBI pathology. The metabolic perturbations carried by consumption of fructose under the threshold for establishment of metabolic syndrome exacerbates the disruptive effects of TBI on glucose metabolism, inflammation and lipid peroxidation in the liver. In conclusion, our study uncovers the potential bidirectional interactions between the brain and liver after brain injury. These experimental data suggest that an important aspect of the TBI pathology takes place in the periphery with subsequent repercussions for the brain. The overall results reveal the compelling possibility that a metabolic perturbation carried by diet is a predictor of worse outcome in the pathophysiology of TBI.

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Nanosymposium

541. Traumatic Brain Injury

Location: Room S404

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Presentation Number: 541.09

Topic: C.10. Brain Injury and Trauma

Support: FA8650-17-2-6H10

Title: Aeromedical relevant hypobaria exposure induced oxidative stress in rats with mild traumatic brain injury facilitates homocysteine flux through the transsulfuration pathway: A compensatory mechanism to mitigate the secondary injury process

Authors: *F. TCHANTCHOU[1], C. MILLER[2], F. LI[1], L. RAMSUE[1], M. GOODFELLOW[1], G. FISKUM[1];
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Abstract: Homocysteine (hcy) is a neurotoxic stress biomarker. It is continuously eliminated and contributes to glutathione synthesis through the transsulfuration pathway. Increased hcy levels were found in people who stayed at high altitude starting at 7500 ft. Similarly, injured service members are often aeromedically evacuated at high altitude (8000 ft) for advanced medical care. Herein, we studied the effects of aeromedical relevant hypobaria (HB) exposure on hcy metabolism and related oxidative stress markers. Male Sprague Dawley rats (~300g) were subjected to mild traumatic brain injury (mTBI) by Controlled Cortical Impact (CCI) method over the left parietal cortex or sham surgery. The next day, they were exposed, for 6 hours, to experimental HB at 8000 ft and 28% oxygen or to normobaria (NB) as control. Thereafter, rats (n = 8/group), were tested for anxiety-like behavior by Plus Maze test and for working memory performance by Y maze test. Other rats (6/group) received intraperitoneal injections of 2-dihydroethidium (HDE, 6mg/kg), to ROS track formation just before HB or NB exposure. Plasma and brain tissues were collected at different time points for histological and biochemical analyses. Statistical analysis was performed by one-way ANOVA with Tukey-Kramer post-test analysis. Measurement of plasma hcy showed a two-fold reduction in both CCI and sham rats 24 hours post-HB compared to NB shams ($p < 0.05$). Moreover, hcy was undetectable in HB-rats 2-hours post-exposure. By contrast, there was a significant increase of malondialdehyde levels in these rat plasma compared to NB CCI and sham rats ($p < 0.01$). Similarly, brain sections of these HB CCI rats showed greater number of HDE incorporated cells compared to HB sham rats ($p < 0.01$) and NB CCI rats ($p < 0.05$). This was associated with 2.5-fold increase in oxidized glutathione ($p < 0.05$). Lesion volume measurements found it was relative increased in HB-CCI rats 24-hours post-exposure. Brain injury lesion was significantly resolved in both HB and NB CCI rats at day 30 post-exposure ($p < 0.01$). Behavioral assessments showed that HB exposure

significantly worsened anxiety like behavior in CCI rats more than a week post-exposure, compared to NB shams ($p < 0.05$). HB exposure had no effect on working memory. In summary, HB exposure skewed hcy elimination through the transsulfuration pathway, resulting in increased glutathione oxidation in response to HB induced oxidative stress. Increased injury lesion by HB was resolved 30 days after, suggesting that increased hcy metabolic contribution to glutathione synthesis represents a compensatory neuroprotective mechanism to mitigate the effects of HB exposure on mTBI neuropathology.

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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.10

Topic: C.10. Brain Injury and Trauma

Support: R01 NS094527
R01 NR013601
1R01NS110635

Title: The voltage-gated proton channel Hv1 impairs recovery after traumatic brain injury in mouse through altered responses of microglia/macrophage

Authors: ***J. WU**[1], J. HE[2], Y. LI[2], R. M. RITZEL[2], B. SHIM[2], A. I. FADEN[3], L.-J. WU[4]; [1]Anesthesiol., Univ. of Maryland, Sch. of Med., Baltimore, MD; [3]Anesthesiol., [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Mayo Clin., Rochester, MN

Abstract: The voltage-gated proton channel Hv1 can rapidly remove protons from depolarized cytoplasm and is highly expressed in the immune system. In the mouse brain, Hv1 is expressed by microglia but not neurons or astrocytes. Microglial Hv1 regulates intracellular pH and aids in NADPH (NOX)-dependent generation of ROS (reactive oxygen species). However, neither the cellular mechanisms nor critical role of Hv1 in the pathophysiology of traumatic brain injury (TBI) are fully understood. In the present study, we report a rapid and persistent up-regulation (12 folds at 7-day and 4 folds up to 1 month) of Hv1 mRNA in the injured cortex after a moderate controlled cortical impact (CCI) in male mice. Hv1 protein expression was elevated 3-4-folds at 7 days and sustained up to 1-month post-injury. qPCR, flow cytometry, and IHC analysis showed that depletion of Hv1 in KO mice significantly attenuated the production of NOX2/ROS and pro-inflammatory cytokines (TNFα, IL1β, and NOS2), however, increased a battery of anti-inflammatory cytokines. Assessment of fine motor coordination using a beam walk test demonstrated better motor performance in Hv1 KO/TBI vs WT/TBI mice. In a battery

of neurobehavioral tests, WT/TBI mice displayed significant cognitive deficits as demonstrated by reduced % spontaneous alternation in Y maze test, reduced time with novel object in Novel Object Recognition test, and reduced time in platform quadrant in Morris Water Maze test. In contrast, Hv1 KO/TBI mice did not display significant deficits in any cognitive test, indicating improved learning and memory performance. Furthermore, the functional improvement in Hv1 KO/TBI mice was associated with decreased cortical lesion volume and reduced infiltration of F4/80 macrophages. Taken together, our data indicate an important role for Hv1 in regulating NOX2/ROS-mediated functional damage post-TBI.

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Nanosymposium

541. Traumatic Brain Injury

Location: Room S404

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 541.11

Topic: C.10. Brain Injury and Trauma

Title: The novel class of homeostatic lipid mediators, elovanoids, provide high-grade neuroprotection in experimental traumatic brain injury

Authors: ***L. S. BELAYEV**[1], A. OBENAUS[2], E. HADDAD[2], L. KHOUTOROVA[1], V. A. CRUZ FLORES[3], P. MUKHERJEE[1], N. A. PETASIS[4], N. BAZAN[1];
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Abstract: Traumatic brain injury (TBI) often leads to substantial cognitive impairments and permanent disability. Recently, we reported the discovery and characterization of a novel class of homeostatic lipid mediators termed elovanoids (ELV), which are derivatives from very long chain polyunsaturated fatty acids (VLC-PUFAs,n-3). ELVs display neuroprotective bioactivities both *in vitro* neuronal injury models and *in vivo* experimental ischemic stroke. The purpose of this study was to determine whether treatment with ELV (ELV-34:6) would be beneficial in a rat model of TBI. Male SD rats (450-400g) were anesthetized with 3% isoflurane, mechanically ventilated, physiologically regulated, and subjected to moderate right parieto-occipital parasagittal fluid-percussion injury. ELV (300 µg/per rat) or saline treatment was administered i.v. at 1 h after TBI (n=5-6 per group). Behavior was evaluated on days 1, 2, 3, 7, and 14 after TBI; a grading scale of 0-12 was employed (normal score=0, maximal deficit=12). *Ex vivo* T2WI of the brains was conducted using 11.7T MRI on day 14 and brain volumes including CA1, CA3, dentate gyrus (DG) and white matter connectivity (diffusion tensor imaging, DTI) was analyzed. The physiological variables were comparable between the four groups. There were no adverse

side effects after ELV administration. Treatment with ELV improved the behavioral scores on day 2, 3, 7, and 14 by 20, 23, 31, and 34% compared to saline treatment. ELV treatment preserved hippocampal volume loss in the CA3 by 4% and DG by 10%. Whole brain tractography (brain and cerebellum) revealed that, in the ELV-treated rats, there were increased numbers of cortical fibers at the injury site. Using a single ROI placed in the ipsilateral corpus callosum (CC) (injured hemisphere) there were increased numbers of streamlines (tracts) with increased connectivity to the contralateral hemisphere in the ELV-treated compared to the saline group. Directionally encoded fractional anisotropy maps demonstrated preservation of the cortex and improved CC integrity. Thus, ELVs protect the integrity of the gray and white matter with improved behavioral outcomes and have promising potential for clinical applications.

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Nanosymposium

541. Traumatic Brain Injury

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Presentation Number: 541.12

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01 NS050465

Title: Probiotic therapeutics prevent neurological and cognitive deficits in traumatic brain injury in mice

Authors: *W. Z. AMARAL, L. Z. YING, F. GOMEZ-PINILLA;
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Abstract: The pathology of Traumatic Brain Injury (TBI) often extends beyond the brain, disrupting multiple peripheral organ systems and affecting global metabolism. Because abnormalities in bowel function are common among brain injury patients, gut dysfunction and dysbiosis have been suggested to play a role in the development of the global TBI pathology. The gut microbiota plays a potent bidirectional role in the gut-brain axis, and the dysbiotic gut is directly implicated in the development of neurological, metabolic and inflammatory disorders. We hypothesize that gut dysbiosis contributes to the TBI pathogenesis and that it represents a novel therapeutic target for treating the peripheral and central effects of brain injury. C57 mice were pre-treated with probiotics or placebo for three weeks and submitted to a mild Fluid Percussion Injury (FPI), a model of concussive injury, or sham surgeries. A probiotic formulation, comprised of *L. helveticus* and *B. longum*, has been previously shown to provide neuronal and cognitive benefits to the rodent brain, and were used as a preventative treatment for the pathology induced by FPI. We present evidence that the gut microbiota is disrupted after FPI,

and that the dysbiotic gut may mediate the effect of FPI on hepatic and systemic glucose metabolism, with a concurrent enrichment of the *Erypelotrichaceae* family and impoverishment of the *Oscillospira* genus. These specific microbiotic changes have been previously implicated in metabolic disorders. FPI also caused memory deficits in the mice, which were prevented by the probiotic treatment. We also examed the physiological pathways that mediate the effect of this probiotic formulation on the brain in the context of TBI. Our data show that the gut microbiota plays important roles in the peripheral sequelae of TBI, and that commensal manipulations can protect the brain and behavior from the impact of TBI. These data are critical to understanding the role of the gut microbiome and gut-brain axis in the TBI pathogenesis, and may result in the novel application of microbiotics in the prevention or reversal of secondary injuries in TBI.

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Nanosymposium

541. Traumatic Brain Injury

Location: Room S404

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 541.13

Topic: C.10. Brain Injury and Trauma

Support: Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development, Rehabilitation Research and Development (I01RX001520))
Assistant Secretary of Defense for Health Affairs through the Congressionally Directed Gulf War Illness Research Program (W81XWH-16-1-0626)
The Veterans Bio-Medical Research Institute
The Bay Pines Foundation

Title: The effects of model repetitive TBI and treatment with tertiary-butylhydroquinone and pioglitazone

Authors: *W. A. RATLIFF[1], D. QUBTY[2], V. DELIC[3], C. G. PICK[2], B. A. CITRON[3,4];
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Abstract: Traumatic brain injury is the signature affliction of military forces serving in recent conflicts with approximately 15% of Operation Iraqi Freedom and Operation Enduring Freedom veterans having received at least one TBI. Among all populations, most TBIs are mild, however even mild injuries, especially when repeated, can result in long term cognitive deficits for which there is no effective treatment. Improved outcomes have been demonstrated in our previous

examinations of treatment with tert-butylhydroquinone (tBHQ), that can activate transcription factor Nrf2, in both *in vitro* and *in vivo* models of injury. Additionally, neuroprotective effects have been demonstrated following treatment with the transcription factor PPAR-γ agonist, pioglitazone, in models of TBI and neurodegeneration. In an effort to better understand the underlying mechanisms of mild TBI and how to treat it, we tested repetitive injury and a combination treatment, containing both tBHQ and pioglitazone, with mice exposed to five closed head injuries with one week intervals between injuries. The treatment was administered intraperitoneally at 30 min after each injury and the brains were collected for examination at eight weeks after the last injury. We have previously reported gene expression, behavioral, and dendritic spine changes using this model. To further investigate alterations within the brain, coronal sections were examined for microglia by Iba1 immunoreactivity and dendritic arbors were evaluated by Golgi staining. We found that the repetitive mild injury resulted in total dendritic lengths reduced by about 10% ($P<0.05$). With treatment, this reduction appeared to be partially reversed. Along with our previously reported behavioral data and regulatory changes, the responses induced by the injury are ameliorated to various extents by our combination treatment. Through continued examination of this model, we hope to better define these neurodegenerative processes and the effects of our treatment to improve outcomes for TBI patients.

Disclosures: W.A. Ratliff: None. **D. Qubty:** None. **V. Delic:** None. **C.G. Pick:** None. **B.A. Citron:** None.

Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

Location: Room N228

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 542.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Ontario Institute of Regenerative Medicine (OIRM)
Wings for Life
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Canadian Institutes of Health Research (CIHR)

Title: Rescuing the fate of neural progenitor transplants in the injured spinal cord niche via attenuation of notch signaling with GDNF

Authors: *M. KHAZAEI[1], C. S. AHUJA[2], H. NAKASHIMA[1], N. NAGOSHI[3], J. WANG[1], J. CHIO[1], A. BADNER[1], M. G. FEHLINGS[4];
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Abstract: Neural progenitor cell (NPC) transplantation is a promising strategy for the treatment of spinal cord injury (SCI). However, optimum integration of cells into the host tissue has been a key challenge for translating this approach to the clinic. In this study, we show that injury-induced Notch activation in the spinal cord microenvironment biases the fate of transplanted NPCs toward reactive astrocytes. In a screen for potential clinically relevant factors to modulate Notch signaling, we identified glial cell-derived neurotrophic factor (GDNF). GDNF attenuates Notch signaling by mediating DLK1 Delta-Like 1 Homolog (DLK1) expression. When transplanted into rodent model of cervical SCI, GDNF-expressing human induced pluripotent stem cell derived-NPCs (hiPSC-NPCs) demonstrated a differentiation bias toward a neuronal fate. In addition, expression of GDNF promoted endogenous tissue sparing and enhanced electrical integration of transplanted cells, which collectively resulted in improved neurobehavioural recovery. CRISPR knockouts of the DLK1 gene in GDNF-expressing hiPSC-NPCs attenuated the effect on functional recovery, demonstrating that this effect is partially mediated through DLK1 expression. These results represent a mechanistically-driven optimization of hiPSC-NPC therapy to redirect transplanted cells toward a neuronal fate and enhance their integration.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

Location: Room N228

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 542.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Intramural research program of the Eunice Kennedy Shriver NICHD at the NIH.

Title: Myelination of peripheral nerves is controlled by phosphatidylinositol 4-kinase type III-beta (PI4KB) through regulation of Schwann cell Golgi function

Authors: *A. ALVAREZ-PRATS[1], T. BABA[1], Y. KIM[1], D. ABEBE[2], S. WILSON[5], Z. ALDWORTH[3], M. A. STOPFER[3], J. HEUSER[4], T. BALLA[1];
[1]Section on Mol. Signal Transduction, [2]Res. Animal Mgmt. Br., [3]Section on Sensory Coding and Neural Ensembles, [4]Section on Integrative Biophysics, NIH, Bethesda, MD; [5]Lab. Animal Services, GlaxoSmithKline, Research Triangle Park, NC

Abstract: Phosphatidylinositol 4-kinase beta (PI4KB) is a Golgi-associated lipid kinase that regulates lipid exchange between the ER and the Golgi and controls vesicular transport out of the Golgi. Within this organelle, PI4KB produces phosphatidylinositol 4-phosphate (PI4P), phosphoinositide that controls delivery of ceramide, glycosyl ceramide and cholesterol from the

ER to the Golgi. Likewise, myelin formation requires a specific distribution of lipids and proteins which need to be properly coordinated to build a functional myelin sheath and to allow an optimal conductivity along the nervous system. Specifically, within the peripheral nervous system (PNS), myelinating Schwann cells (SCs) surround mostly axons of motor neurons, while non-myelinating SCs surround smaller diameter axons, which belong mainly to sensory neurons. Here we describe peripheral myelination defects caused by SC-specific deletion of PI4KB in mice. Sciatic nerves of such mice showed thinner myelin that selectively affected large diameter axons and gross aberrations in myelin organization affecting the nodes of Ranvier, the Schmidt-Lanterman Incisures and Cajal bands. Non-myelinating SCs also showed an inability to wrap thin nerve fibers. Likewise, SCs of sciatic nerves of mutant mice showed a distorted Golgi morphology and a reduced localization and dispersion of the oxysterol binding protein (OSBP), an important PI4P-regulated cholesterol transport protein, in the already shrunk Golgi compartment. Moreover, GOLPH3, another important PI4P effector, was completely lost from the Golgi in mutant nerves. Accordingly, the cholesterol content of sciatic nerves was greatly reduced and so was the number of caveolae observed in SCs. Although the conducting velocity of sciatic nerves of mutant mice showed a 70% decrease, the mice displayed only subtle impairment in their motor functions. Importantly, PI4KB was not only localized to the perinuclear Golgi in sciatic nerves of control mice, but it was prominently enriched in the nodes of Ranvier, associated with the SC microvilli. This contrasted with the lack of localization of either the Golgi markers giantin or gm130, or the two PI4P effectors, OSBP and GOLPH3 in this compartment in sciatic nerves of the mutant mice. Strikingly, the microvilli were almost completely missing in the nodes of Ranvier of these animals together with a reduced actin staining within the same compartment. These studies highlight the critical role of PI4KB in proper myelination through its support of SC Golgi functions related to lipid metabolism, protein glycosylation and organization of microvilli in the nodes of Ranvier of peripheral nerves.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

Location: Room N228

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 542.03

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Extracellular vesicles derived from neural progenitor cells - A preclinical evaluation in a mouse model of stroke

Authors: *T. R. DOEPPNER, X. ZHENG, I. GRAF, R. KRUSE, M. BÄHR;
Neurol., Univ. of Göttingen Med. Sch., Göttingen, Germany

Abstract: Stem cells such as mesenchymal stem cells (MSCs) and neural progenitor cells (NPCs) increase neuroregeneration and neurological recovery after stroke. However, grafted cells are not integrated into residing neural networks, but mediate these effects by secretion of extracellular vesicles (EVs). EVs are a heterogeneous group of vesicles that are secreted by eukaryotic cells, containing different proteins and non-coding RNAs. Nevertheless, current data is exclusively based on the application of MSC-derived EVs under stroke conditions. We therefore evaluated the therapeutic potential of NPC-derived EVs under conditions of in vitro hypoxia and in vivo cerebral ischemia. As such, EVs were applied to cerebral organoids that have been exposed to hypoxia followed by reoxygenation under standard cell culture conditions. EV treatment under these conditions significantly reduced cell death rates of organoids in comparison to control organoids. To investigate the effects of NPC-EVs in vivo, EVs were systemically delivered to mice on days 1, 3, and 5 post-stroke in mice that were allowed to survive for 84 days. EVs significantly reduced post-stroke brain injury on day 84, which was associated with a better neurological outcome in the corner turn test and the tight rope test. In this context, application of EVs under in vivo stroke settings significantly stimulated post-stroke neuroregeneration and axonal plasticity. The present study therefore for the first time provides clinically relevant evidence that NPC-derived EVs are equal to MSC-derived EVs in terms of their therapeutic potential under experimental stroke settings, warranting rapid proof-of-concept studies of NPC-derived EVs in stroke patients.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

Location: Room N228

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 542.04

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Differences in human and animal primary neural stem cell responses to inflammatory and regenerative cues: Impact on the successful translation of therapies to humans

Authors: *A. GALUTA[1], D. GHINDA[2], R. SANDARAGE[1], J. F. KWAN[1], S. CHEN[2,3], A. M. AURIAT[4,3], E. C. TSAI[1,2,3];
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Abstract: Rationale: In animal models of spinal cord injury, inflammation post-trauma activates neural stem and progenitor cells (NSPCs) which differentiate into glial scar astrocytes. To direct NSPC fate and promote regeneration instead, NSPCs can be targeted using growth factors.

However, the mechanisms regulating human spinal cord NSPC pathophysiology and regeneration are not known. **Objective:** To improve the translation of animal therapies for spinal cord injury, we assessed the effect of inflammatory and regenerative factors on primary NSPCs in a small (rat) and large (pig) animal model in comparison to NSPCs from humans. **Methods:** Primary spinal cord NSPCs from adult humans (n=8), pigs (n=5) and rats (n=6) were cultured using the neurosphere assay. To mimic post-injury inflammation, primary derived NSPCs were treated with pro-inflammatory factors interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), or transforming growth factor-β (TGFβ). To direct regeneration, NSPCs were treated with retinoic acid (RA), platelet derived growth factor (PDGFα), or bone morphogenic protein-(BMP4) to induce neurons, oligodendrocytes or astrocytes, respectively. Cultures were treated for 7 or 14 days, fixed, and characterized by immunocytochemistry (GFAP, β-iii tubulin, O4, and BrdU). To track proliferation, BrdU was added 24 hours prior to fixation. **Results:** IL-6, TNFα and TGFβ induced astrogenesis of rat NSPCs (3.9±0.7, 5.0±0.9, and 4.0±0.6 fold, respectively) after 7 days concomitant with reduced neurogenesis (0.14±0.90, 0.07±0.04, 0.07±0.05 fold, respectively). Pig NSPCs similarly increased astrogenesis (1.38±0.04, 1.26±0.05, and 1.45±0.04 fold, respectively) but after 14 days of treatment. On the contrary, human NSPCs had reduced astrogenesis (0.14±0.07, 0.6±0.2, and 0.12±0.07 fold, respectively) over the course of 14 days, but generated more neurons (1.23±0.05 and 1.34±0.04 fold, respectively) with IL-6 and TGFβ treatments. With regenerative factor treatment, RA increased neuron differentiation of both human and rat NSPCs, PDGFα increased oligodendrocyte differentiation of only rat NSPCs, and BMP4 increased astrocyte differentiation of human and rat NSPCs at low (40 ng/mL) and high (100 ng/mL) concentrations, respectively. **Conclusion:** For the first time, we have directly compared human, pig and rat spinal cord NSPC response to pathophysiological and regenerative factors and determined cell-intrinsic differences in behaviour. Improved understanding of these differences between human and animal models will be important for the successful translation of regenerative therapies to humans.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

Location: Room N228

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 542.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01EB007615
Reeve Foundation ES1-2011
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Title: Epidural stimulation elicits network-level activation of human spinal circuitry to generate rhythmic motor behavior in individuals with motor complete spinal cord injury without intentional supraspinal input

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Abstract: Introduction and Methods: Mammalian spinal circuitry has the intrinsic capacity to generate repetitive rhythmic patterns in the absence of supraspinal input. Epidural stimulation over the lumbosacral spinal cord can access and enhance this intrinsic capacity. To better understand human spinal circuitry's capacity to generate complex rhythmic patterns when functionally isolated from supraspinal input, we studied responses to epidural stimulation in individuals with chronic motor complete SCI (n=19; age: 29.5 ± 8.7 yrs; time post-injury: 4.8 ± 2.7 yrs; 84% male, 12 AIS A, 7 AIS B). Study procedures were approved by the University of Louisville IRB. All subjects provided informed consent. We used a 5-6-5 electrode array and stimulator implanted epidurally over spinal cord segments L1 - S1. Neurophysiological spatial-temporal mapping involved recording bilateral EMG activity over multiple leg extensor and flexor muscles while varying stimulation frequency, pulse width (450 and 1000 μs), amplitude, and combinations of active anode and cathode array contacts. Results: We frequently observed rhythmic, alternating bilateral activity of leg flexors (iliopsoas and tibialis muscles) at approximately 0.5 Hz when stimulating at 30 Hz and 1000 μs pulse widths. Notably, rhythmic leg muscle activity was not synchronized to stimulation pulses. When stimulating at 2 Hz, we also observed rhythmic bursts of both flexor and extensor muscles that occurred both in synchronization with the stimulation pulses and in a few cases at a lower frequency. Discussion: These results suggest that epidural stimulation can access human spinal cord networks differentially based on temporal and spatial features of bipolar stimulation. Furthermore, the fact that rhythmic leg muscle activity was elicited at a different frequency than that of extrinsic stimulation indicates that epidural stimulation likely activates intrinsic spinal networks rather than simple mixtures of dorsal afferent nerve roots. This occurs in the absence of intentional supraspinal input. We predict that when applied at subthreshold intensities, properly configured epidural stimulation targeted at network-level excitation may result in the best conditions for motor recovery.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Prolonged effects of targeted epidural stimulation on blood pressure and cerebral blood flow velocity during tilt: A case report

Authors: *J. M. WECHT[1], A. V. OVECHKIN[2], S. WANG[3], B. DITTERLINE[4], O. BLOOM[5], J. D. GUEST[6], G. F. FORREST[7], S. J. HARKEMA[8];
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Abstract: Introduction: Severe spinal cord injury (SCI) results in cardiovascular dysfunction including orthostatic hypotension and concomitant cerebral hypo-perfusion that results in symptoms such as dizziness and lightheadedness and orthostatic intolerance. We previously reported that targeted lumbosacral spinal cord epidural stimulation for cardiovascular function (CV-scES) increased orthostatic blood pressure and mitigated intolerance in 4 individuals with SCI. The effects of a prolonged CV-scES intervention on orthostatic tolerance and hemodynamic stability has not been reported. Methods: One individual with chronic cervical motor-complete SCI who had significant cardiovascular dysfunction was implanted with a 16-electrode array on the dura (L1-S1 cord segments, T11-L1 vertebrae). A 70° head-up tilt test was performed prior to implantation and after 40- and 80-sessions of an individualized CV-scES training intervention, which was programmed to maintain seated systolic blood pressure within a targeted range without eliciting skeletal muscle activity of the lower extremities. Beat-to-beat systolic blood pressure (SBP) was assessed using photoplethysmography and transcranial Doppler ultrasound was used to assess beat-to-beat cerebral blood flow velocity (CBFv) in the middle cerebral artery

at supine rest and during the tilt, which was conducted for 30-minutes, or until symptom limited, without active CV-scES. Results: Prior to implantation the participant was able to tolerate only 70 seconds of tilt. After 40- and 80-sessions of CV-scES training the participant was able to tolerate the full 30-minutes at 70° without active CV-scES stimulation. Prior to implant SBP fell 37 mmHg (35%) from supine to tilt, which was associated with a fall in CBFv of 30 cm/s (46%). After 40-sessions of CV-scES training, the fall in SBP was comparable (-40 mmHg; 36%) but the fall in CBFv was attenuated (-8 cm/s; 16%) during head-up tilt without active stimulation. After 80-sessions of CV-scES training, the fall in SBP (-5 mmHg; 5%) and the fall in CBFv (-2 cm/s; 5%) were mitigated during head-up tilt without active stimulation. Conclusion: This case report demonstrates the prolonged and sustained effect of a targeted CV-scES training intervention on SBP and CBFv, which resulted in improved orthostatic tolerance without the need for active stimulation and suggests plasticity in autonomic cardiovascular regulation in persons with chronic severe SCI.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

Location: Room N228

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 542.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: UW Neurological Surgery

Title: 3D printed polypyrrole microneedle arrays for electronically controlled drug release

Authors: J. HUANG[1], J. JOHNSON[2], M. WALTER[2], ***R. SAIGAL**[3];
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Abstract: Spinal cord and traumatic brain injuries (SCI and TBI) result in secondary injury causing further damage to neural cells, due to mechanisms of inflammation and cytotoxicity. Though some anti-inflammatory drugs have shown promising results in reducing secondary injury in animal models, there is no proven therapeutic drug for human SCI/TBI. Steroids are controversial in clinical practice due to systematic side effects at the required high dosage with questionable efficacy. An electrically controlled drug release system would allow for spatiotemporal control of drug delivery and might solve some of the issues with systemic dosing. We designed and fabricated a polypyrrole (PPy) microneedle array for control release of dexamethasone for application to the nervous system. Conductive microneedles were fabricated on a silicon substrate in IP-S using a microscale 3D printer, then sputter-coated in gold. Dexamethasone-loaded PPy is deposited onto the microneedles from a solution of 0.2M pyrrole,

0.2M sodium dodecylbenzenesulfonate, and 30mg/ml dexamethasone (Dexa). Dexa release from the PPy microneedles were tested in an in vitro model of neuroinflammation. Mouse BV2 microglia cells were seeded for 24h, then activated by with lipopolysaccharide (LPS) and interferon gamma (IFN). One hour after activation, cells received treatments and controls (Dexa actively released from PPy at -1V x 2min, blank PPy with active release, Dexa PPy with passive release, Dexa solution, or no treatment). There were also no cells and unactivated cells as controls. The release devices were then removed, and the cells incubated for 48 hours. A Griess assay was used to test nitric oxide production, and a Luminex multiplexing assay used to test for production of inflammation factors and cytokines. Active release of Dexa from the PPy microneedles was found to significantly reduce the production of nitric oxide and interleukin-1b in activated microglia. The microneedles were also tested in an in vitro transdural model, in which the needles were used to deliver Dexa across a collagen dura substitute. Mass spectometry analysis of initial studies showed successful dexamethasone release across the the dura from electronically stimulated PPy microneedles, while little transdural release was found when Dexa solution is used without microneedles. These results suggest electronically controlled release of dexamethasone from our PPy microneedles is capable of mitigating neuroinflammation. The microneedles also demonstrate the ability to deliver dexamethasone across a dural membrane.

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Nanosymposium

542. Therapeutic Interventions for Nervous System Injury

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Presentation Number: 542.08

Topic: C.11. Spinal Cord Injury and Plasticity

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FRC 2017
R01EB016629-01

Title: Anatomy and function of the vertebral column lymphatics network in mice

Authors: ***J.-L. THOMAS**[1], L. JACOB[2], L. BOISSERAND[3], L. GERALDO[4], J. BRITO[2], T. MATHIVET[4], S. ANTILA[5], K. ALITALO[5], N. RENIER[2], A. EICHMANN[4];
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Abstract: Cranial lymphatic vessels (LVs) are involved in transport of fluids, macromolecules and central nervous system (CNS) immune responses. Little information about spinal LVs is available, because these delicate structures are embedded within vertebral tissues and difficult to visualize using traditional histology. Here we reveal an extended vertebral column LV network

using three-dimensional imaging of decalcified iDISCO+-clarified spine segments. Vertebral LVs connect to peripheral sensory and sympathetic ganglia and form metameric vertebral circuits connecting to lymph nodes and the thoracic duct. They drain the epidural space and the dura mater around the spinal cord and associate with leukocytes. Vertebral LVs are VEGF-C-dependent and remodel extensively after spinal cord injury. VEGF-C-induced vertebral lymphangiogenesis exacerbates the inflammatory responses, T cell infiltration and demyelination following focal spinal cord injury. Therefore, vertebral column LVs add to skull meningeal LVs as gatekeepers of CNS immunity and may be potential targets to improve the maintenance and repair of spinal tissues.

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Nanosymposium

543. New Approaches for Pain Assessment and Treatment

Location: Room S405

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 543.01

Topic: D.03. Somatosensation – Pain

Title: National institute of neurological disorders and stroke preclinical screening platform for pain

Authors: *S. A. WOLLER[1], J. H. KEHNE[3], M. HACHICHA[2], B. KLEIN[4], M. A. PELLEYMOUNTER[6], M. L. OSHINSKY[7], W. J. KOROSHETZ[8], A. TAMIZ[5], S. IYENGAR[1]; [1]DTR, [2]NINDS, Rockville, MD; [3]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [4]NIH/NINDS, Rockville, MD; [5]NIH/NINDS, Bethesda, MD; [6]Div. of Translational Res., NINDS/NIH, Rockville, MD; [7]Systems & Cognitive Neurosci., NINDS/NIH, Bethesda, MD; [8]NIH, Bethesda, MD

Abstract: The NIH recently launched the Helping to End Addiction Long-term (HEAL) Initiative, a trans-agency effort to provide scientific solutions to the opioid crisis. One aim of the HEAL Initiative is to reduce the reliance on opioids by advancing research to improve pain management. With HEAL support, NINDS has developed the Preclinical Screening Platform for Pain (PSPP) to facilitate the identification of non-addictive treatments, including small molecules, biologics, devices, and natural products, for acute and chronic pain conditions.
The overall goal of the PSPP is to provide researchers from academia and industry, in the US and internationally, an efficient, rigorous, one-stop *in vivo* screening resource to accelerate identification and efficacy profiling of non-opioid therapeutics for the treatment of pain. Under NINDS direction, preclinical testing of submitted agents is performed by contract facilities on a blinded and confidential basis at no cost to the PSPP participants. Test candidates are evaluated

in a suite of *in vivo* pain-related assays following *in vitro* receptor profiling, pharmacokinetic and safety assessment. Importantly, test candidates are also evaluated in models of abuse liability.
A key feature of the PSPP is the flexibility to acquire and validate innovative animal models that more closely represent human pain conditions, including headache, and to use these models to test and characterize promising non-addictive therapeutic candidates submitted by the research community.
Screening in the PSPP will be a key step in transitioning HEAL preclinical programs into clinical programs directly aligned with the HEAL Initiative goal of "accelerating the discovery and preclinical development of non-addictive pain treatments."

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Nanosymposium

543. New Approaches for Pain Assessment and Treatment

Location: Room S405

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 543.02

Topic: D.03. Somatosensation – Pain

Support: SRPBS from MEXT/AMED
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AMED Brain/MINDS

Title: Sustainable reduction of phantom limb pain by MEG-based BMI

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Abstract: Background: Phantom limb pain is an intractable pain that reduces patient quality of life. Our previous study demonstrated that training with a brain-machine interface (BMI) to control a
robotic hand increased the classification accuracy of phantom hand movements in association with increased pain and suggested that reducing this classification accuracy may reduce phantom limb pain. Here, we developed a novel BMI to control a virtual hand image of the patient's phantom hand and trained the patient with the BMI for 3 consecutive days to assess the efficacy of the BMI treatment to reduce pain.
Methods: A single-blinded randomized crossover trial was performed at Osaka University Hospital. Twelve patients with chronic phantom limb pain of an upper limb participated in the trainings. For each patient, we first constructed a real decoder that classified intact hand movements based on the patient's cortical motor currents estimated by magnetoencephalographic signals. A virtual hand images were controlled by the output of the real decoder. Patients were trained to control the hand image by moving the phantom hand for three days (real training). Then, in the random training, patients engaged with the same hand image, but the image was controlled by randomly changing values. The order of two trainings were randomly assigned. Pain, the primary indicator in this study, was evaluated using a visual analogue scale (VAS) before and after each training session and for a further follow-up period of 17 days.
Results: VAS at day 4 was significantly reduced from baseline after real training (45.3 [24.2] to 30.9 [20.6], 1/100mm, mean [SDs]; p=0.009), but not after random training, with a significant difference (p=0.048). Compared to day 1, VAS scores were significantly reduced by 32% at day 4 and 36% at day 8 after the real training, and were significantly lower than scores after the random training (p<0.01). The decoding accuracy of the phantom hand was significantly decreased after the real training, which correlated with pain reduction at day 4 (R=0.58).
Conclusions: A 3-day BMI training to control a virtual image of the phantom hand significantly reduced pain for at least a week. We suggest that ongoing BMI training may further decrease phantom limb pain by gradually attenuating the representation of the phantom hand.

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Nanosymposium

543. New Approaches for Pain Assessment and Treatment

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Presentation Number: 543.03

Topic: D.03. Somatosensation – Pain

Support: Canadian Institutes of Health Research – Foundation Grant #353649

Title: Use of dicer-substrate small interfering RNA *in vivo* to decipher the time-related contribution of the CCL2/CCR2 signaling in chronic inflammatory and neuropathic pain

Authors: *M.-A. DANSEREAU[1,2], K. NESZVECSKO[1], A. M. JACOBI[3], S. S. ROSE[3], M. A. BEHLKE[3], J.-M. LONGPRE[1], P. SARRET[1];
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Abstract: Chronic pain is a debilitating condition that seriously affects the quality of life of more than 20% of people worldwide. Despite extensive efforts, the therapeutic options remain currently limited. As our knowledge of this complex disease increases and the need for new treatments gets critical, the field is moving towards new approaches favoring targets specific to different aetiologies of chronic pain. Hence, we investigated the potential of dicer-substrate small interfering RNA (DsiRNA) encapsulated in lipid nanoparticles (LNPs) to identify key contributors and their role in the progression of chronic pain.
Our first step was to evaluate the delivery and efficacy of DsiRNA encapsulated in LNP administered intrathecally (i.t.) to male Sprague-Dawley rats. Western blot analysis showed a knockdown of 91% of the PTEN targeted protein in the L4-L6 lumbar dorsal root ganglia (DRG) with no apparent knockdown in the spinal cord. Subsequently, rats were subjected to either chronic inflammatory pain induced by an intraplantar administration of complete Freund's adjuvant (CFA) or neuropathic pain through chronic constriction of the sciatic nerve (CCI). i.t. delivery of 27-mer DsiRNA (5 µg) designed against the CCL2 chemokine or its main receptor, CCR2 was then performed for two consecutive days at different temporal windows: before (prophylactic treatment), one day after, or at a later time point (day 7 for CFA, day 25 for CCI) following induction of chronic pain conditions. Mechanical hypersensitivity was assessed on a weekly basis using von Frey filaments. Repeated i.t. injections of DsiRNA targeting CCL2 or CCR2 were more effective in reducing the mechanical hypersensitivity in CFA-treated rats when administered one day after pain induction rather than used prophylactically. Furthermore, neither DsiRNA was able to reverse the mechanical hypersensitivity, when administered 7 and 8 days post-CFA. In CCI-treated rats, only the invalidation of CCR2 was effective in decreasing tactile allodynia when administered one day after CCI surgery. Interestingly, the DsiRNA against CCR2 also significantly reversed mechanical hypersensitivity in neuropathic pain state for 3 weeks when administered 25 and 26 days post-CCI.
These results demonstrate that the role of the CCL2/CCR2 axis varies in a time dependent-manner and differs based on the chronic pain aetiology. Similar approaches using encapsulated DsiRNA in LNP could also provide invaluable information for other proteins contributing to nociception and analgesia, helping to develop more specific and effective therapeutic avenues.

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Nanosymposium

543. New Approaches for Pain Assessment and Treatment

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Presentation Number: 543.04

Topic: D.03. Somatosensation – Pain

Support: Aircast Foundation Inc.
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Title: Using place preference to evaluate pain relief in a rat model of chronic low back pain

Authors: B. YUAN[1,3], J. LI[1], A. L. PERSONS[2], D. CHEN[1], **A. CHEE**[1], *T. C. NAPIER[2], H. S. AN[1];
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Abstract: Opioids are potent analgesics that uniquely reduce subjective aspects of pain, yet these agents are highly addictive. Our research focuses on identifying non-opioid analgesics that can provide relief from chronic, low back pain. We propose that place conditioning can be used to identify such compounds, and here we used morphine to provide proof-of-concept. We induced chronic back pain in male Sprague-Dawley rats (375-400g, n=10), by injuring intervertebral discs at levels L3/4, L4/5 and L5/6 using a 21-gauge needle followed by injection of lipopolysaccharide. Control rats underwent sham surgery wherein discs were exposed but not injured (n=8). X-rays taken before surgery and 6 weeks post-surgery verified injury; disc height was reduced to 78±10% of baseline in the injured rats, whereas height was 98±9% in shams (unpaired t-test; $p<0.05$). Pain severity was assessed using von Frey filaments to test hindpaw hyperalgesia before surgery, and 1, 2, 3 and 5 weeks post-surgery. Compared to shams, hindpaw withdrawal thresholds decreased significantly at all post-surgical time points in rats that had disc injury (two-way rmANOVA; $p<0.001$). Four weeks after surgery, we tested the hypothesis that morphine would produce conditioned place preference (CPP) in injured rats using protocols that were not sufficient to do so in sham rats. The CPP protocol involved a pretest on day 1, a single saline exposure (1mL/kg, sc) in one unique context followed by a single morphine exposure (10mg/kg, sc) in a different context on day 2, and on day 3, treatment-free rats were allowed access to both contexts. Compared to pretest, disc-injured rats demonstrated a significant increase in time spent in the morphine-paired context ($p=0.01$; paired t-test) on day 3, whereas sham rats did not show a place preference ($p>0.05$) indicating a lack of morphine reward associative learning. By inference, CPP by the drug-free, injured rats may reflect the memory of pain relief as was obtained during morphine-conditioning. These findings suggest that single-pairing CPP may be an effective means to identify therapeutic candidates for chronic back pain.

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Nanosymposium

543. New Approaches for Pain Assessment and Treatment

Location: Room S405

Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 543.05

Topic: D.03. Somatosensation – Pain

Title: Prevention of neuropathic pain development via a therapeutic plasma fraction

Authors: *M. CASTRO LABRADA, L. MADUSHANI, R. ESTRADA, I. GALLAGER, S. BRAITHWAITE, V. KHEIFETS;
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Abstract: Persistent neuropathic pain (NP) is a frequent consequence of peripheral nerve injuries. The elderly population with chronic pain in the US is estimated to reach 70 million by 2030, and the development of novel non-opioid therapies is paramount. We previously demonstrated that a human plasma fraction (PF) can reverse age-related decline of neurogenesis and neuroinflammation. As neuropathic pain has been shown to further exacerbate these mechanisms, PF may be beneficial to prevent downstream consequences. In the present study, we focused on the impact of PF on the microglial state, hippocampal neurogenesis and behavioral parameters in a model of pain in aged mice. Chronic Constriction Injury model (CCI) was used to induce NP like behaviors in 22-month-old C57/BL6 mice. We observed that mice subjected to CCI developed significant reduction in pain threshold as measured via mechanical allodynia and thermal hyperalgesia that persisted for 5 weeks. PF administration significantly ameliorated these behavioral effects 2 weeks after surgery and the beneficial effect was maintained for the duration of the study. In addition to behavioral changes, NP was also accompanied by microglial activation in the CNS, changes in astrocytes within the dentate gyrus and decrease in neurogenesis. These changes were attenuated with PF treatment as observed histologically 5 weeks post-surgery. Taken together, these data suggest that neuropathic pain-behavior in aged mice is accompanied by neuroinflammation and decline in neurogenesis, which can be prevented by PF treatment. These findings are deepening our mechanistic understanding of the multifactorial, regenerative properties mediated by circulating proteins in the blood. They also provide a rationale for the development of this novel plasma fraction as therapy for neuropathic pain.

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Nanosymposium

543. New Approaches for Pain Assessment and Treatment

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Time: Tuesday, October 22, 2019, 1:00 PM - 3:00 PM

Presentation Number: 543.06

Topic: D.03. Somatosensation – Pain

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NIH/NCI CA20676901

Title: Diode laser based selective assessment (DLss) of A-δ or C-fiber nociception: From cells to patiens

Authors: *M. J. IADAROLA[1], D. C. YEOMANS[2], **M. I. NEMENOV**[4,3];
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Abstract: Single fiber recording of C- or Aδ nociceptive fibers is a precise method for investigating underlying pain mechanisms. However, clinical accessibility of this method is limited. Selective assessment of C- or Aδ fiber nociceptive activity would provide information on the differential contribution of these fibers to pain, pain pathophysiology and the response to analgesic agents. However, currently available tests simultaneously activate both fiber types in unpredictable proportions. Thus, there is an unmet need for an accessible and highly translatable method for differential fiber stimulation. Aim: to evaluate diode laser selective activation of Aδ or C-fiber thermonociceptors (DLss) in animals, humans, and single neurons to probe mechanisms underlying different pain states, as well as for development of a novel pain treatments. In contrast to contact, radiant heat, or CO_2 laser stimulation which heat skin surface, 980 nm DLss homogeneously and reproducibly heats the epidermis to dermis. Selective C-fiber activation is achieved with pulse duration of 1 and 20 sec, & beam diameter 5 mm. Aδ fiber activation is achieved with pulse duration of 50 to 200 ms & beam diameter 1 to 2 mm. DLss stimulation of TRPV1-positive HEK & DRG cells *in vitro*produces inward currents and reproducible action potentials. In animal behavioral studies, selective nociceptor activation is defined by the latency (C-fibers) or threshold DLss intensity (A-δ-fibers) of evoked muscle twitch or limb withdrawal. In humans, reported sensation, fMRI and MEG imaging, cortical laser evoked potentials and neurogenic flare demonstrate selective nociceptor activation. In response to C-fiber DLss, volunteers and pain patients uniformly report single modality tonic burning pain; for Aδ DLss - subjects uniformly report only phasic pricking pain. Consistent with these sensory reports, conduction velocity measurements are consistent with Aδ or C-fibers. Patients with painful peripheral neuropathy generally report cutaneous numbness and increased heat pain thresholds when measured using contact heat. However, pain thresholds measured with DLss showed fairly normal C-fiber pain thresholds, but significantly increased Aδ heat pain

thresholds. Thus, diabetic sensory loss is fiber-type specific. We have developed and rigorously tested DLss for selective activation of A-δ or C fiber nociceptors. The results have shown remarkable consistency across multiple paradigms, including single cell electrophysiology, animal behavioral testing, human volunteers, and pain patients; DLss can provide unique and critical information for improvement of pain management.

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543. New Approaches for Pain Assessment and Treatment

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Title: Unlocking NaV1.7's pain potential: Discovery and initial characterization of a novel class of compounds selectively targeting NaV1.7 through inhibition of a protein-protein interaction

Authors: ***R. KHANNA**[1,2,3,4], R. CHAWLA[2], A. CHEFDEVILLE[1], S. CAI[1], A. MOUTAL[1], J. YU[1], X. YANG[1], E. DUSTRUDE[1], C. MADURA[1], S. S. BELLAMPALLI[1], L. CHEW[1], S. LUO[1], L. FRANÇOIS-MOUTAL[1], D. D. SCOTT[1], V. GOKHALE[1,2], M. KHANNA[1,3]; [1]Univ. of Arizona, Tucson, AZ; [2]BIO5 Institute, Univ. of Arizona, Tucson, AZ; [3]The Ctr. for Innovation in Brain Sciences, The Univ. of Arizona Hlth. Sciences, Tucson, Arizona, Tucson, AZ; [4]Regulonix Holding Inc., Tucson, Arizona, Tucson, AZ

Abstract: NaV1.7 is a key ion channel in pain signaling. Gain-of-function mutations in the human NaV1.7 gene produce sensory neurons hyperexcitability associated with severe pain; whereas loss-of-function mutations generate congenital insensibility to pain syndromes. However, efforts to develop NaV1.7 inhibitors for pain therapeutics have consistently failed. Post-translational modifications of NaVs and/or auxiliary subunits and protein-protein interactions have been reported as NaV-trafficking mechanisms. We recently reported that modification of the axonal collapsin response mediator protein 2 (CRMP2) by a small ubiquitin-like modifier (SUMO) controls both trafficking and currents of NaV1.7 (Dustrude *et al., J. Biol. Chem.* 288: 24316-31 (2013)). Capitalizing on this unique pathway for NaV1.7 regulation, Regulonix Holding Inc. identified compounds by computationally docking 50,000 small molecules to a pocket encompassing the residue SUMOylated (K374) in CRMP2. These

compounds were designed to inhibit the E2-conjugating enzyme Ubc9-CRMP2 interaction, which, in turn, would block CRMP2 from being SUMOylated by Ubc9. Among the over 266 compounds identified in this manner, several (*i*) exhibited superb inhibition of the Ubc9-CRMP2 interaction, (*ii*) bound to CRMP2 - but not Ubc9, and notably, (*iii*) did not affect any other CRMP2-mediated functions, including facilitation of neurite outgrowth, ability to bind to protein partners (tubulin, N-type voltage-gated calcium (CaV2.2), and N-methyl-D-aspartate receptor (NMDAR)), and ability to regulate CaV2.2 activity. Superb anti-allodynic activities without loss of motoric performance or sympathetic side effects were observed for several compounds. Furthermore, animal pharmacological studies indicated that some of the compounds displayed extended duration of action (2-16-fold) compared with morphine upon intrathecal administration to rats. Additional studies demonstrated inhibition of NaV1.7 currents in human and porcine sensory neurons, thus increasing likelihood of translational success and 'de-risking' compound selection. Thus, we advance an innovative approach by focusing on a unique mechanism of action of the compounds that involves an indirect targeting to control surface expression and activity of the NaV1.7 channel.

Disclosures: **R. Khanna:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regulonix Holding Inc.. **R. Chawla:** None. **A. Chefdeville:** None. **S. Cai:** None. **A. Moutal:** None. **J. Yu:** None. **X. Yang:** None. **E. Dustrude:** None. **C. Madura:** None. **S.S. Bellampalli:** None. **L. Chew:** None. **S. Luo:** None. **L. François-Moutal:** None. **D.D. Scott:** None. **V. Gokhale:** None. **M. Khanna:** None.

Nanosymposium

543. New Approaches for Pain Assessment and Treatment

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Topic: D.03. Somatosensation – Pain

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UAVenture Capital

Title: Unlocking NaV1.7's pain potential: Preclinical studies on a first-in-class selective NaV1.7 regulator

Authors: *A. CHEFDEVILLE[1], R. CHAWLA[1], S. CAI[1], A. MOUTAL[1], M. PATEK[2], J. YU[1], X. YANG[1], E. T. DUSTRUDE[1], C. MADURA[1], S. S. BELLAMPALLI[1], L. CHEW[1], S. LUO[1], L. FRANÇOIS-MOUTAL[1], D. D. SCOTT[1], V. GOKHALE[1], M. KHANNA[1], R. KHANNA[1]; [1]Univ. of Arizona, Tucson, AZ; [2]BrightRock Path LLC, Tucson, AZ

Abstract: NaV1.7 sodium channel is a prized target for pain therapeutics since mutations in the human gene, *SCN9A*, have been reported to produce both too much pain - due to gain-of-function mutations - or no pain - due to loss-of-function mutations. But despite these genetic links, development of NaV1.7 inhibitors has been unsuccessful. Our approach exploits an alternative strategy of regulating NaV1.7 function through a protein-protein interaction. We had reported that the tubulin-binding Collapsin Receptor Mediator Protein 2 is necessary for the maintenance of NaV1.7 currents in sensory neurons; and that preventing addition of a SUMO protein at [position] K374, either through a lysine to alanine mutation or via a cell membrane penetrant "decoy' peptide, efficiently decreased NaV1.7 membrane localization and reversed neuropathic pain. After extensive screening (see poster by Khanna et al.), we identified a small molecule, AZ194, that (i) bound CRMP2, (ii) prevented its SUMOylation, (iii) induced NaV1.7internalization, and (iv) reduced NaV1.7 currents in rodent dorsal root ganglia (DRG) neurons. AZ194 belongs to a class of benzoylpiperidin-4-yl-2-benzimidazoles and features drug-like segments connected in L-shaped topology. To further validate the binding hypothesis of AZ194 and to fine-tune its physico-chemical properties, a set of analogs has been designed reflecting pharmacophore features of the series and typical ADME and PK parameters. As an early "de-risking" step, >50% blockade of NaV1.7 currents by 500 nM AZ194 was recapitulated in porcine and human sensory neurons. Importantly, AZ194 - at 20 μM - did not inhibit other NaV1.x channels; N-type (CaV2.2) voltage-gated calcium or human ether-a-go-go (hERG) potassium channels and did not bind to opioid receptors. Intrathecal administration of AZ194 reversed mechanical allodynia in rat models of nerve-injury induced pain, chemotherapy-induced peripheral neuropathy, and HIV-associated peripheral sensory neuropathy. AZ194 did not compromise locomotion, nor did it induce anxiety or depressive-like behaviors. Long-term dosing revealed no abnormalities under histopathological analyses. Its selectivity for NaV1.7 and broad efficacy across several pain models make AZ194 a lead candidate for pain therapeutic development.

Disclosures: **A. Chefdeville:** None. **R. Chawla:** None. **S. Cai:** None. **A. Moutal:** None. **M. Patek:** None. **J. Yu:** None. **X. Yang:** None. **E.T. Dustrude:** None. **C. Madura:** None. **S.S. Bellampalli:** None. **L. Chew:** None. **S. Luo:** None. **L. François-Moutal:** None. **D.D. Scott:** None. **V. Gokhale:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regulonix Holding Inc. **M. Khanna:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regulonix Holding Inc. **R. Khanna:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regulonix Holding Inc..

Nanosymposium

544. Motor Control and Stroke Recovery

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Title: Premotor cortical tDCS enhances inter-hemispheric motor network functional connectivity in chronic stroke patients

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Abstract: *Background.* Patients with chronic stroke frequently have varying degrees of unilateral upper limb paresis. In order to enhance motor recovery, non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have traditionally aimed to enhance excitability of the ipsilesional primary motor cortex (iM1). Despite some initial success, the effects of targeting iM1 with tDCS have been inconsistent, especially when patients with severe paresis are included. It is thought that patients with severe paresis may lack viable corticospinal substrates originating from iM1 and instead use alternate substrates for motor recovery. The premotor cortex (PMC) may represent a target for modulating motor network excitability due to its dense inter- and intra-hemispheric connections as well as its significant contributions to the descending corticospinal tract. The objective of the proposed study was to use resting-state functional MRI (rs-fMRI) to assess changes in inter- and intra-hemispheric motor network functional connectivity (FC) stemming from constraint-induced movement therapy (CIMT) paired with iPMC tDCS.
Methods. 18 subjects underwent rs-fMRI and were randomized to receive 5 weeks of CIMT combined with excitatory iPMC tDCS or sham stimulation. Rs-fMRI seeds were placed in the iM1 and dorsal premotor cortex (iPMd), and FC to the ipsilesional and contralesional M1, PMd, and supplementary motor areas (SMA) was reported as a Z-score. All ROIs were informed by task-based fMRI activation.
Results. Following the intervention, there was a mean 4.8 (SD 4.2) point increase in Upper Extremity Fugl-Meyer (UEFM) score across participants, however there were no differences between the tDCS and sham groups. Rs-fMRI analysis demonstrated a significant increase in iPMd-iM1 FC across all participants (Z-score: pre-intervention = 0.54, post-intervention = 1.23; $F(1,14) = 7.12$, $p = 0.018$). Post hoc analysis demonstrated a significant increase in iPMd-cPMd FC only in participants with moderate to severe baseline paresis in the tDCS group compared to sham (change in Z-score: tDCS = 0.83, sham = -0.84; $p = 0.009$). Increases in iPMd-cPMd FC were correlated with improvements in proximal UEFM score only in subjects with moderate to

severe paresis (r = 0.623, p = 0.041).
Conclusions. We provide preliminary evidence that targeting iPMC can enhance inter-hemispheric FC for participants with severe paresis. This distinct pattern of enhanced FC may be associated with improvements in proximal motor impairment. Future studies should explore the utility of iPMC tDCS for improving motor recovery specifically in the more severe chronic stroke population.

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Nanosymposium

544. Motor Control and Stroke Recovery

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Topic: E.04. Voluntary Movements

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Title: Chronic stroke hemispheric dominance and task specific fMRI laterality of cortical motor activation

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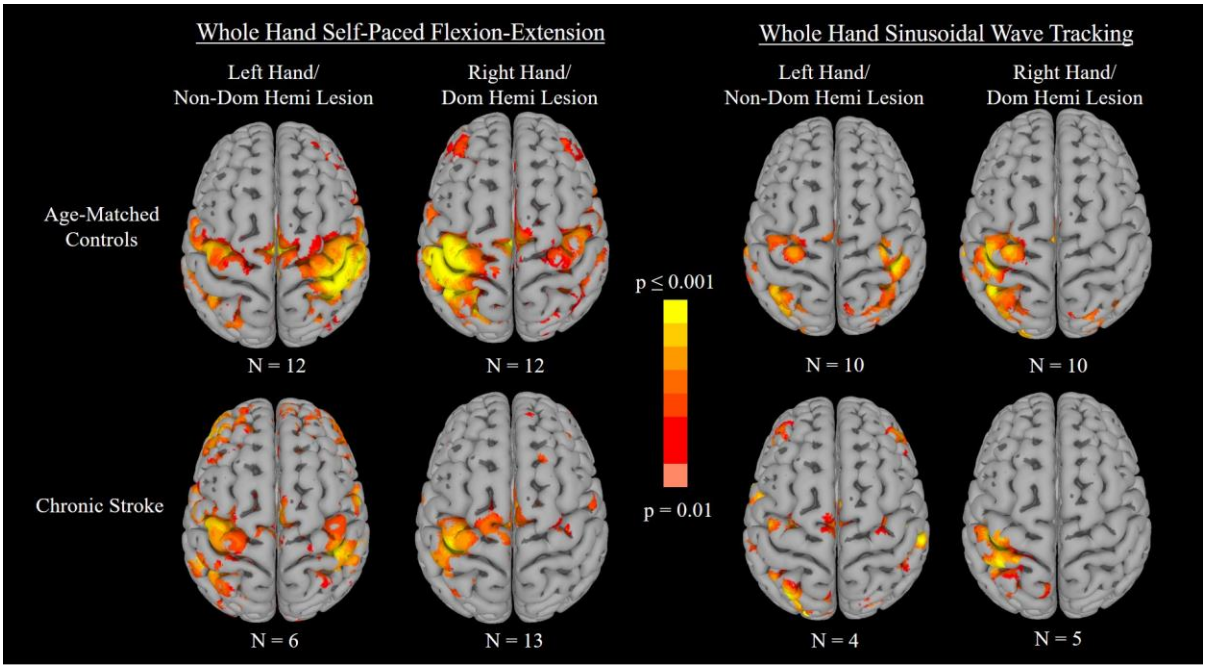
Abstract: Chronic stroke fMRI studies suggest that greater lateralized activity in the ipsilesional hemisphere during movement of the impaired upper-limb is associated with better motor outcomes, whereas bilateral activation is associated with poorer motor outcomes. These studies help inform therapeutic research interventions that aim to promote motor recovery by increasing activity of the ipsilesional hemisphere and decreasing activity of the contralesional hemisphere through methods of non-invasive brain stimulation and forced practice of the impaired upper-limb. But, recovery following these interventions is variable, suggesting that solely targeting hemispheric laterality may not be the most efficacious approach. Factors that may influence laterality index and its usefulness in predicting motor disability are hand dominance relative to the impaired upper-limb and the task performed during fMRI. Our objective was to explore whether laterality of cortical motor activation can, in part, be explained by hemispheric

dominance and task specificity, similar to previous able-bodied studies. Twenty-eight, right handed participants with chronic hemiplegia and 22 age-matched able-bodied participants performed either whole-hand self-paced flexion-extension (N = 19) or whole-hand sinusoidal wave tracking (N = 9) of the impaired limb inside the scanner. Group fMRI analysis revealed broad activation patterns within the higher motor, motor, and parietal regions for both tasks and greater laterality during dominant hand tracking. However, overall, there is greater bilateral activation in participants with non-dominant hemisphere lesions, and these results are comparable to non-dominant hand movements within the controls. These results may explain the variance in recovery following therapies that aim to increase activity in the ipsilesional hemisphere and may offer alternative therapeutic cortical targets dependent on impaired hand dominance and task specificity.



Disclosures: **D.A. Cunningham:** None. **A.O. Rickert:** None. **E.B. Plow:** None. **J.S. Knutson:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

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Title: Using TMS to inform paradigms of DBS in human stroke motor recovery

Authors: *K. O'LAUGHLIN[1], E. B. PLOW[2], T. ARORA[3], A. WYANT[1], D. A. CUNNINGHAM[7], K. A. POTTER-BAKER[1], Y.-L. LIN[8], R. GOPALAKRISHNAN[4], D. P. FLODEN[4], K. B. BAKER[5], A. G. MACHADO[6];
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Abstract: Brain stimulation is a promising experimental technique to promote upper limb motor recovery in stroke. But outcomes achieved in severe patients are rather limited. Conventional approaches target the residual motor cortices in hopes of restoring original connectivity, but this fails when damage is extensive. Our group is investigating whether a new approach targeting the cerebellar dentate nucleus using deep brain stimulation (DBS) could enhance outcomes by capitalizing on viable, excitatory disynaptic connections. This translational effort is supported by more than a decade of preclinical work showing that dentate DBS induces positive therapeutic benefits in ischemic stroke models in association with gains in motor cortical excitability, synaptogenesis and functional re-mapping. Six patients (<2yrs post-stroke) with severe motor impairment (Fugl-Meyer, FM < 33) have received DBS in conjunction with rehabilitation for 4 months after reaching a plateau in motor performance with rehabilitation alone. Assessment of motor impairment (FM) and neurophysiology is being completed at many time-points before, during and after DBS + Rehab. Neurophysiology is being tested with non-invasive brain stimulation - Transcranial Magnetic Stimulation (TMS). TMS is being paired with DBS for the first time to 1) guide patient selection through pre-surgical confirmation of corticospinal pathway viability - the best predictor of therapeutic-response, 2) inform clinical programming by measuring acute, DBS-induced changes in motor cortical excitability, and 3) characterize changes in cortical excitability and remapping of motor networks as a function of treatment-related gains. Preliminary results have revealed achievement of therapeutic response (clinically meaningful reduction in impairment, 4 to 33 point FM gain) in 4 out of 6 patients. TMS has revealed the acute facilitatory effect of dentate DBS on ongoing motor cortical activity at short-latencies (2-5ms), consistent with the disynaptic nature of underlying connections, and thus helped identify optimal DBS settings for chronic application (acute 30Hz DBS ON vs. OFF, p= 0.03). TMS has also revealed similar gains in motor cortical excitability and functional re-mapping as witnessed previously in animal studies (6% to 26% reduction in TMS current required and 5- to 8-point gain in number of motor cortical sites producing criterion response in weak muscles). Therefore, targeting intact cerebellum in the presence of severe stroke-related injury may have therapeutic benefits and synergy between DBS and TMS has the potential to offer comprehensive and dynamic understanding of underlying mechanisms.

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Nanosymposium

544. Motor Control and Stroke Recovery

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Title: Uncovering the role of intact, contralesional motor cortices in upper limb functional motor recovery after stroke

Authors: *E. B. PLOW[1], Y.-L. LIN[5], V. SANKARASUBRAMANIAN[6], K. A. POTTER-BAKER[7], D. A. CUNNINGHAM[8], K. O'LAUGHLIN[1], A. CONFORTO[9], K. SAKAIE[2], X. WANG[3], J. S. KNUTSON[8], A. G. MACHADO[4];
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Abstract: The role of intact, contralesional motor cortices in chronic upper limb motor recovery after stroke is widely debated. Their role was originally assumed to be *inhibitory* towards paretic limb movement (‘transcallossal inhibition’ or TCI), but recent evidence suggests their role may be *compensatory*, providing alternate uncrossed/bilateral connections in severe ipsilesional injury. A new model known as the ‘bimodal balance recovery hypothesis’ tries to reconcile evidence suggesting that contralesional influence may be *inhibitory* or *compensatory* depending on the severity of corticospinal injury/impairment. But this model remains to be validated and a criterion severity level stratifying patients with differing contralesional influences is yet to be identified. This knowledge is essential to develop tailored treatments. Therefore, we performed two studies to (1) characterize how contralesional influence varies across the range of severity and identify the criterion severity level stratifying patients with differing influences, and (2) determine how stratified patients respond to contralesional excitation vs. suppression with brain stimulation. Twenty-five patients with mild to severe impairment participated in study 1 and another 24 participated in study 2 (chronic, >6mths). Transcranial Magnetic Stimulation (TMS) was used to measure TCI and corticospinal excitability. In study 2, repetitive TMS (rTMS) was given for 1 session each to suppress (1Hz) and excite (5Hz) cortices. Functional motor improvements in reaching response were studied. Study 1 revealed a parabolic relationship

between TCI and impairment (Fugl-Meyer, FM, best =66). In patients with FM >43, TCI was higher with lower FM, while in patients with FM <43, TCI was lower with lower FM. Our results suggest that the nature of contralesional influence is bimodal- inhibitory in less severe and less inhibitory in more-severe patients; FM 43 (confidence interval 40-46) can stratify patients with differing influences. Study 2 validated this criterion by showing that patients with FM >43 respond to contralesional suppression via gain in residual corticospinal excitability, while patients with FM <43 respond to contralesional excitation via further reduction in TCI. Therefore, study 2 confirms that contralesional motor cortices are inhibitory in less-severe patients because removing their effect disinhibits residual excitability and permits better movement, while these cortices are compensatory in more severe patients because enhancing their activity reduces TCI and elicits motor improvement. Our findings have implications for design of precise, effective treatments.

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Nanosymposium

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Topic: E.04. Voluntary Movements

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Title: Modulation of post-movement event-related synchronization by deep brain stimulation of the dendatothalamocortical pathway in stroke patients

Authors: *R. GOPALAKRISHNAN[1], K. B. BAKER[2], D. A. CUNNINGHAM[4], N. D. MATHEWS[2], B. A. CAMPBELL[2], A. G. MACHADO[1,3];
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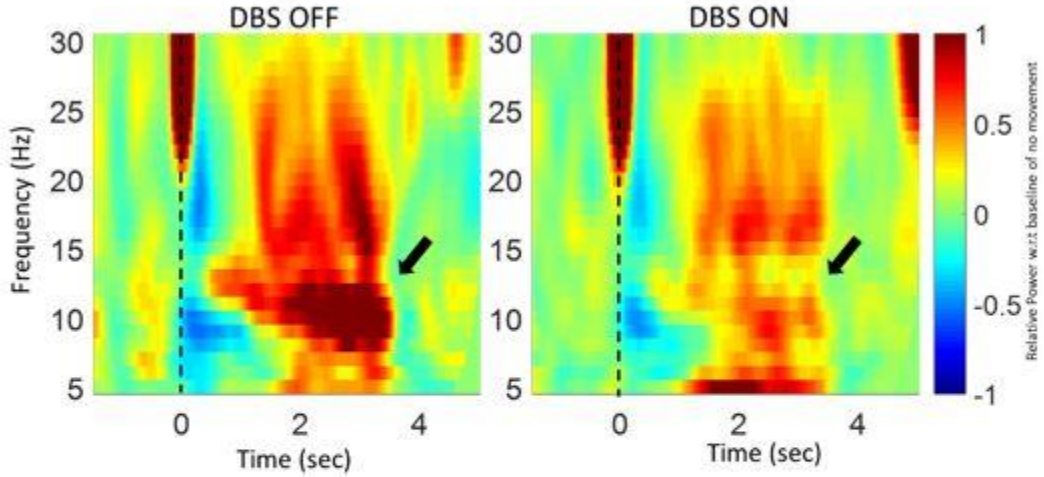
Abstract: Introduction: Stroke is a leading cause of serious long-term disability in the United States and the industrialized world. Despite progress in acute interventional strategies, there continues to be an enormous need for novel approaches to facilitate rehabilitation for patients facing chronic, residual post-stroke hemiparesis. We are currently investigating deep brain stimulation of the dentatothalamocortical pathway (DN-DBS) that exploits natural neural

pathways in order to modulate cerebral cortical activity via thalamocortical connections (Machado et al, 2013). To facilitate therapeutic programming, we examined the acute effects of DN-DBS on cortical excitability during the execution of motor tasks. We adopted a well-established model based on EEG called the post-movement Event-Related Synchronization (ERS) to quantify the power change in alpha and beta frequency bands over the perilesional cortex (Pfurtscheller et al., 1996). Recent research has found the amplitude of ERS to be a robust surrogate marker of percentage effort and rate of force development during the execution of motor tasks (Fry et al. 2016). Methods: During a grip squeeze task, stroke patients followed visual cues that indicated a preparatory phase, a contraction phase, and a relaxation phase. The tasks were performed on an average of 70 trials using a dynamometer while EEG was acquired continuously, for both DBS OFF and ON conditions. The percentage effort during the task was set to ~20% maximal voluntary force elicited by the patients during the OFF condition, and was kept constant between DBS OFF and ON conditions. Results: We found that stroke patients exhibited increased ERS amplitude at baseline (DBS OFF), and DBS ON significantly reduced ERS amplitude. Conclusions: The results show not only the modulation of cortical excitability by DN-DBS, but also possible facilitatory effects of DN-DBS when optimal stimulation parameters (contact location, current and pulse width) were used. Future work will correlate task behavior and ERS modulation to further substantiate the observed findings.



The effects of DN-DBS on ERS during a grip squeeze task. Figure shows a time-frequency plot of DN-DBS induced modulation in the alpha band (8 – 12 Hz) ERS between 2 – 4 secs after movement onset (dashed lines) on affected extremity over the perilesional motor cortex. X-axis is time in secs, Y-axis is frequency in Hz, and colormap is magnitude of power change with respect to baseline period of -1.5 to -1 secs. Black arrow points to the strong ERS during DBS OFF (left) that was suppressed by DBS ON (right).

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Nanosymposium

544. Motor Control and Stroke Recovery

Location: Room S403

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 544.06

Topic: E.04. Voluntary Movements

Support: NIH NICHD grant K01HD079584
NIH NICHD grant K12HD055931

Title: Disruption of direct and indirect descending pathways in post-stroke individuals: Effects of stimulation timing and activation state

Authors: *A. J. LOPEZ, J. XU, J. LIU, M. TREES, M. R. BORICH, T. M. KESAR;
Rehabil. Med., Emory Univ., Atlanta, GA

Abstract: Both direct and indirect descending corticofugal pathways that project onto spinal lower motor neurons (LMNs) have an important role in motor control. Stroke causes disruption in descending modulation of spinal circuits that contribute to elevated spinal circuit excitability. However, if and to what extent stroke impacts the excitability of direct and indirect descending pathways remains unclear. Paring sub-threshold transcranial magnetic stimulation (TMS) with peripheral nerve stimulation (PNS) at specific inter-stimulus intervals (ISIs) induces facilitation of the Hoffman's reflex (H-reflex). Short latency facilitation (SLF) of the H-reflex measures the excitability of direct, fast-conducting descending pathways; long-latency facilitation (LLF) measures the excitability of indirect, polysynaptic, slower-conducting descending pathways. Preliminary findings from our lab show a reduction in SLF and LLF post-stroke. The purpose of this ongoing study was to investigate the effect of ISIs and activation state on post-stroke SLF and LLF. To date, as part of this ongoing study, data have been collected on 5 post-stroke individuals >6-months post-stroke. Here, results from 3 stroke survivors are reported. Unconditioned H-reflexes were obtained by delivering PNS to the posterior tibial nerve at the intensity that elicited an H-reflex amplitude at 20% Mmax in the soleus muscle. Sub-threshold TMS (90% motor threshold) was delivered to the lesioned hemisphere, with ISIs between PNS and TMS varying from -10 to +50 ms. Comparison of conditioned versus unconditioned H-reflexes at ISIs within the SLF window showed disruption of SLF (%SLF: 90.5 to 99.76%). All 3 stroke survivors showed facilitation in the LLF ISI range (%LLF: 151.97 to 178.9%). Preliminary results also show enhancement of SLF and LLF during the active versus resting motor state. In summary, the loss of SLF post-stroke, shown here at a range of ISIs, indicates disruption of the fast, direct corticospinal pathway. The observation of LLF suggests that indirect, slower-conducting descending pathways, such as the cortico-reticulo-spinal tract, may contribute to post-stroke neuroplasticity, and merit further investigation. Evaluating the influence of functionally-relevant conditions such as activation state and posture on the magnitude of SLF

and LLF may provide novel insights about the role of descending corticofugal pathways in post-stroke motor control.

Disclosures: A.J. Lopez: None. **J. Xu:** None. **J. Liu:** None. **M. Trees:** None. **M.R. Borich:** None. **T.M. Kesar:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

Location: Room S403

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 544.07

Topic: E.04. Voluntary Movements

Support: NIH Grant R01HD075777

Title: Does interhemispheric balance influence ankle motor control in stroke survivors?

Authors: *H. LIM, S. MADHAVAN;
Physical Therapy, Univ. of Illinois At Chicago, Chicago, IL

Abstract: Objective: Ankle motor control deficit has been identified as a significant contributor to impaired walking after stroke. Imbalance in interhemispheric symmetry after stroke, as a result of decrease in ipsilesional and increase in contralesional corticomotor excitability (CME), has been shown to be related to limited upper limb motor control. However, little is known whether the interhemispheric imbalance affects lower limb motor control in stroke survivors. The purpose of this study was to determine the influence of interhemispheric imbalance of the lower limb M1 on the performance of a skilled visuomotor ankle tracking task in chronic stroke survivors.
Methods: Twenty-eight participants with post-stroke hemiparesis participated in this study (22 males/6 females; mean age 60 years; average 5 years post-stroke). Single-pulse transcranial magnetic stimulation (TMS) was used to measure motor evoked potentials (MEP) from both the paretic and nonparetic tibialis anterior muscles (TA). Corticomotor symmetry was calculated as a ratio of the recruitment curve slopes of the paretic and non-paretic, with a value close to 0 indicating greater balance between the hemispheres and 1 indicating more imbalance. Ankle motor control was quantified by the ability of participants to track a sinusoidal target using dorsiflexion-plantarflexion movements of the paretic ankle. Tracking accuracy was calculated over an average of 3 minutes of tracking.
Results: Mean tracking accuracy was 67.9% (SD=13.0). Mean corticomotor symmetry ratio of 0.56 (SD=0.32); the lesioned M1 demonstrated 58% less CME when compared to non-lesioned M1. Pearson correlation revealed no significant correlation between corticomotor asymmetry and ankle tracking accuracy (r=.168, p=.394). Ankle tracking accuracy was negatively correlated with CME of the lesioned M1 (r=-.421, p=.026).

Conclusion: Our results indicate that interhemispheric corticomotor symmetry is not associated with paretic ankle motor control. Paradoxically, we noted that participants with reduced CME of the lesioned M1 demonstrated greater tracking accuracy. A possible explanation maybe that other descending pathways, for example the reticulospinal tract, may have been upregulated in these participants. Future studies are recommended to further investigate the role of other descending motor pathways that may contribute to cortical control of lower limb motor control.

Disclosures: H. Lim: None. **S. Madhavan:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

Location: Room S403

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 544.08

Topic: E.04. Voluntary Movements

Support: AHA Grant 18PRE33960555 (AS)

Title: Can aerobic exercise modulate corticomotor excitability in stroke?

Authors: *A. SIVARAMAKRISHNAN[1], S. MADHAVAN[2];
[1]Univ. of Illiois At Chicago, Chicago, IL; [2]Physical Therapy, Univ. of Illinois At Chicago, Chicago, IL

Abstract: Background: Aerobic exercise has shown to facilitate neuroplasticity of the primary motor cortex (M1) in healthy individuals. A single bout of aerobic exercise can improve hand motor skill learning and corticomotor excitability in healthy individuals. However, the effects of aerobic exercise on neuroplasticity after stroke are still not completely understood. Moreover, the neurophysiological mechanisms that drive neural plasticity following aerobic exercise and its effects on the lower limb M1 are unknown. Here, we sought to investigate the effects of aerobic exercise on descending corticomotor excitability, intracortical, and transcallosal inhibition of the lower limb M1 in stroke survivors.
Methods: 16 individuals with chronic stroke (age range 45 - 69) underwent a single session of moderate intensity ((50 - 65% of Heart Rate Maximum) aerobic exercise on a recumbent stepper (20 minutes total, 5 minutes warm up and cool down). Electromyography data was obtained from bilateral tibialis anterior muscles in response to single pulse transcranial magnetic stimulation (TMS). TMS related outcome measures included recruitment curve slopes (80 % active motor threshold (AMT) - 140% AMT), short interval intracortical inhibition (SICI) and ipsilateral silent period (iSP) (an index of transcallosal inhibition) before and after exercise.
Results: Preliminary findings in 16 subjects did not reveal a significant change in any of the TMS measures. We observed a trend towards a decrease in SICI (around 2 - 4 %) and an increase in iSP duration (11 - 15 ms) from baseline. Changes in motor evoked potential

recruitment curve slopes were small (around 9 - 12%).
Conclusions: Our findings suggest that a single session of exercise may not demonstrate modulation of the excitability of the descending corticomotor pathways or the interneuronal circuits. We will conduct a future study to evaluate the effects of exercise on intracortical and transcallosal inhibition in a larger cohort of participants. Further work is required to examine exercise interventions as priming adjuncts to conventional rehabilitation for stroke survivors.

Disclosures: A. Sivaramakrishnan: None. **S. Madhavan:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

Location: Room S403

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 544.09

Topic: E.04. Voluntary Movements

Support: NSERC RGPIN 2015

Title: The effect of glucose levels on TMS-evoked afferent inhibition: A placebo-controlled, double-blinded intervention study

Authors: *C. V. TURCO, S. TOEPPE, A. J. NELSON;
Kinesiology, McMaster Univ., Hamilton, ON, Canada

Abstract: The integrity of the sensorimotor system can be probed indirectly by pairing peripheral nerve stimulation and transcranial magnetic stimulation (TMS). The evoked phenomenon is known as short- and long-latency afferent inhibition. Though a common measure in TMS research, it is unknown whether dietary factors such as circulating glucose impact the measure of afferent inhibition. The purpose of the present study was to investigate the influence of glucose on afferent inhibition. Nineteen healthy individuals participated in this three-way crossover, placebo-controlled, double-blinded intervention study. Individualized latency of peak blood glucose was obtained following intake of a 75g glucose drink during a familiarization session. Individuals then completed three sessions where they received one of the following interventions: 75g glucose drink, sucralose-sweetened drink or water. Short- and long-latency afferent inhibition were assessed before, and at 30 min and ~60 minutes post-intervention corresponding to the latency of peak blood glucose and at the presumed peak of glucose levels in the cerebrospinal fluid, respectively. The results show that both short- and long-latency afferent inhibition were not affected by any of the three interventions, indicating that elevated blood glucose levels do not impact afferent inhibition.

Disclosures: C.V. Turco: None. **S. Toeppe:** None. **A.J. Nelson:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

Location: Room S403

Time: Tuesday, October 22, 2019, 1:00 PM - 4:00 PM

Presentation Number: 544.10

Topic: E.04. Voluntary Movements

Support: CAPES
CNPq

Title: Motor and synaptic deficit in 5-lipoxygenase knockout mice

Authors: *M. B. DA SILVA[1], R. CAMPOS[1], J. FRANÇA[1], P. FROST[2], J. CLARKE[2], V. RIBEIRO-RESENDE[1], C. CANETTI[1];
[1]Inst. of Biophysics, [2]Sch. of Pharm., Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil

Abstract: The 5-Lipoxygenase (5-LOX) is an essential enzyme in the synthesis of leukotrienes and lipoxins. It is widely expressed in cells involved in the regulation of inflammation, allergies and other immune responses. However, recent works show that central nervous system (CNS) neurons express high levels of 5-LOX, although the physiological role of neuronal 5-LOX remains unclear. The present work aims to evaluate how the absence of 5-LOX enzyme can influence synaptic plasticity, microglial activation and regeneration. For this purpose, 129/sv male adult mice knockout for 5-LOX (5-LO- /) or wild type (5-LO + / +) were used. The basal levels of synaptophysin and PSD95 were evaluated by western blot analysis in the motor cortex and hippocampus of both groups. Synaptophysin levels were significantly higher both in motor cortex and hippocampus of 5-LO - / - animals, when compared to WT animals ($n = 6$; $p < 0.01$). Moreover 5-LO-/- animals show a lower baseline motor performance, assessed by the rotarod test, when compared to WT animals ($n = 10$, $p < 0.01$). In spite of the results obtained in the motor analysis, no differences were observed in the sensorial tests (Von frey hair test, formalin test and hot plate test). Microglial quantification and morphology was evaluated by immunofluo-rescence through labeling Iba-1 protein in the motor cortex and hippocampus, this quantification showing similar results for both 5-LO- / - and WT group.

Disclosures: M.B. Da Silva: None. **R. Campos:** None. **J. França:** None. **P. Frost:** None. **J. Clarke:** None. **V. Ribeiro-Resende:** None. **C. Canetti:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

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Presentation Number: 544.11

Topic: E.04. Voluntary Movements

Support: FRQS 35012
NSERC RGPIN-2017-06120
FRQNT 2018-PR-207644

Title: Paired Associative Stimulation (PAS) in freely-behaving rats did not modulate corticomotor plasticity through volley timing

Authors: *W. K. TING[1], C. MÉRETTE[1], G. PICHER[1], M. HUOT-LAVOIE[1], C. ETHIER[2]; [1]Univ. Laval - CERVO, Québec, QC, Canada; [2]Psychiatrie et Neurosciences, Univ. Laval - CERVO, Quebec, QC, Canada

Abstract: We developed a model of *in vivo* Paired Associative Stimulation (PAS) in freely behaving rodents and tested the hypothesis of spike timing dependent plasticity (STDP) in the motor system. After chronic implantation of electrodes in the motor cortices of ten rats, we used a within-subjects design to test for a normalized increase of Motor Evoked Potential (MEP) integral response resulting from cortical stimulation, after paired stimulation of the cortex and the peripheral muscles. Single pulses of electrical stimulation were delivered to the cortex and the peripheral muscles, paired with a pre-determined offset latency and repeated 300 times at 0.5 Hz. Timing offset conditions were randomized within each animal and the stimulations were timed such that the volleys coincided at the rat motor cortex and spinal cord. We also performed four experimental controls with cortical or muscle stimulation only, full rest, and a paired condition with an inter-stimulus delay not expected to induce STDP-like effects. We analyzed the data with a mixed effect model, using stimulation offset timing and MEP assessment time as factors. Contrary to our primary hypothesis, the data did not support plasticity in motor evoked potential across all offset latencies tested. In summary, we did not identify a robust plastic effect using our PAS intervention. Our results have implications for studying spinal PAS in rodents, noting specifically the high intra- and inter-rat MEP variability in the interpretation of results. We conclude looking forward to future work investigating why PAS, and spike timing modulation, appears to be ineffective in this chronically-implanted, freely-behaving rodent model.

Disclosures: W.K. Ting: None. **C. Ethier:** None. **M. Huot-Lavoie:** None. **C. Mérette:** None. **G. Picher:** None.

Nanosymposium

544. Motor Control and Stroke Recovery

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Presentation Number: 544.12

Topic: E.04. Voluntary Movements

Support: ONR Global (N62909-15-1-2002)
Fondazione Roma (NCDS-2013-00000349)
D1 Funds Università Cattolica

Title: Role of nitric oxide signaling in modulation of mouse motor cortex plasticity induced by transcranial direct current stimulation

Authors: *M. V. PODDA[1], V. LONGO[1], C. COLUSSI[2], S. COCCO[1], M. SPINELLI[1], S. A. BARBATI[1], C. GRASSI[3];
[1]Univ. Cattolica del Sacro Cuore, Rome, Italy; [2]Dept. of Biomed. Sci., Natl. Res. Council (CNR-IBCN), Roma, Italy; [3]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

Abstract: Increasing evidence indicates that anodal transcranial direct current stimulation (tDCS) promotes plastic changes in the targeted brain areas. However, much less is known about the intracellular signaling pathways engaged by tDCS although indirect evidence suggests the involvement of Ca^{2+}. Here we investigated the impact of tDCS on motor cortex glutamatergic synaptic transmission and plasticity focusing on the role played by nitric oxide (NO). Electrophysiological and molecular analyses were performed on C57BL/6 mice subjected to one daily session of anodal tDCS (20 min, 35.4 A/m^2) for 3 consecutive days (3×tDCS) or sham stimulation. Mice subjected to 3×tDCS showed increased long-term potentiation at M1 layer II/III synapses and enhanced basal synaptic transmission, as revealed by input/output protocol. The frequency of miniature EPSCs was increased in layer II/III pyramidal neurons of brain slices from 3×tDCS mice compared to sham-stimulated mice, suggesting that tDCS also affects neurotransmitter release. Molecular analyses showed that the levels of $pCREB^{Ser133}$, $pCaMKII^{Thr286}$ and $pGluA1^{Ser831}$ were all enhanced in the motor cortex of 3×tDCS mice. Furthermore, we found that tDCS activated NO-dependent pathways. Specifically, GluA1 S-nitrosylation was enhanced following 3×tDCS and, more importantly, mouse treatment with the nNOS inhibitor, L-NAME, abolished the tDCS-induced increase of $pGluA1^{Ser831}$, thus suggesting a causative link between the tDCS-promoted GluA1 S-nitrosylation and its phosphorylation. Treatment with L-NAME also abolished the tDCS-induced increase in mEPSCs, indicating that NO mediates the facilitatory action of tDCS on neurotransmitter release from presynaptic terminals. Remarkably, 3×tDCS increased both HDAC2 S-nitrosylation and Bdnf levels, effects that were hindered by L-NAME treatment. Collectively, our data show that anodal tDCS boosts synaptic transmission and plasticity in the motor cortex via post-translational modifications of plasticity-related proteins and increased Bdnf expression. NO emerges as major determinant of these effects that are mediated by GluA1 and HDAC2 S-nitrosylation leading to enhanced GluA1 phosphorylation and gene expression, respectively. Our findings add a critical layer to understanding of molecular mechanisms underlying tDCS effects and provide a rationale for using this strategy to enhance motor performances under physiological conditions and following brain injury.

Disclosures: M.V. Podda: None. **V. Longo:** None. **C. Colussi:** None. **S. Cocco:** None. **M. Spinelli:** None. **S.A. Barbati:** None. **C. Grassi:** None.

Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

Location: Room N227

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 545.01

Topic: H.01. Animal Cognition and Behavior

Support: CIHR grant 340328

Title: Using calcium sensors to monitor synapse number in *Aplysia* sensorimotor neuron cultures

Authors: *W. S. SOSSIN, T. W. DUNN, C. A. FARAH;
McGill Univ., MOntreal, QC, Canada

Abstract: Plasticity at the Aplysia sensorimotor neuron synapse contributes to behavioural habituation and sensitization. This plasticity observed in vivo is also observed at reconstructed synapses between isolated, cultured neurons. While a variety of evidences indicate that some types of plasticity involve changes in the number of individual transmitter release sites participating in the synaptic connection, direct observation of such changes have not been convincingly made. Here we examine the use of a membrane targeted JRGECO or gCAMP6S calcium indicator in the postsynaptic neuron and synaptophysin phluorin in the presynaptic neuron to measure the spatial distribution of the individual synapses participating in the sensorimotor neuron synapse. We provide evidence that we can detect synaptic transmission at the quantal level. We also observe a variety of other non-synaptic calcium transients that appear to be enhanced by stimulation. We will use this method to identify new transmitter release sites participating in synaptic transmission after long-term facilitation of these connections and determine if and how these new synapses formed after plasticity differ from pre-existing synapses.

Disclosures: W.S. Sossin: None. **T.W. Dunn:** None. **C.A. Farah:** None.

Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

Location: Room N227

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 545.02

Topic: H.01. Animal Cognition and Behavior

Support: F.S.B. Miller Fellowship

Title: Isoform specificity of PKMs in long-term facilitation is mediated through stabilization by KIBRA

Authors: *L. FERGUSON[1], W. S. SOSSIN[2];
[2]Dept Neurobiol, [1]McGill Univ., Montreal, QC, Canada

Abstract: Persistent activity of protein kinase M (PKM), the truncated form of protein kinase C (PKC), can maintain long-term changes in synaptic strength in many systems including the marine mollusk, *Aplysia californica.* Moreover, different types of long-term facilitation (LTF) in cultured *Aplysia* sensorimotor synapses rely on the activities of different PKM isoforms in the presynaptic sensory neuron and postsynaptic motor neuron. The kidney and brain expressed adaptor protein (KIBRA) stabilizes PKMs in an isoform specific and activity-independent manner, suggesting a possible mechanism through which the isoform specificity of PKMs is established. Indeed, the isoform specificity of catalytically inactive dominant negative (DN)-PKMs to erase LTF is correlated with isoform specific competition for stabilization by KIBRA. We identify a new conserved region of KIBRA and show that different splice isoforms in this region stabilize different PKMs. We show that it is the isoform-specific sequence of the alpha-helix “handle” of PKMs that allows KIBRA and its splice variant to distinguish between and selectively stabilize the different PKM isoforms.

Disclosures: L. Ferguson: None. **W.S. Sossin:** None.

Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

Location: Room N227

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Presentation Number: 545.03

Topic: H.01. Animal Cognition and Behavior

Support: CIHR PJT-153059
CIHR MOP-133444
NSERC RGPIN-2017-05140

Title: Boundaries on lability: Severe fear learning leads to reconsolidation-resistant memories due to noradrenergic-dependent changes in plasticity mechanisms

Authors: *J. HAUBRICH, K. NADER;
McGill Univ., Montreal, QC, Canada

Abstract: New memories go through a labile period during which they are gradually consolidated into a stable, long-term memory. Recall later on may cause the memory to return to an unstable state where it can be modified (i.e. reconsolidation). However, extreme fear learning can result in memories that are resistant to undergo reconsolidation. Our goal was to determine

how severe fear learning shapes memory formation into a state that is resistant to change. We hypothesize that during highly aversive experiences, unique signals trigger long-lasting molecular modifications that ensure the memory will be stored in a state that lacks the lability mechanisms required to trigger reconsolidation. Using the auditory fear conditioning task, rats were trained with 1 tone-shock pairing to create mild fear memories, or 10 pairings to create strong fear memories. Later, memory was reactivated, and reconsolidation-blockade was conducted. The effectiveness of the treatment was then evaluated in a test 1 day later. One day after the test, animals were sacrificed and the amygdala, the dorsal and the ventral hippocampi were collected for western blot analysis. We found that unlike animals trained in the mild protocol, strongly trained rats were resistant to reconsolidation-blockade. At the molecular level, strong training upregulated GluA2-containing AMPAR and downregulated NR2B-containing NMDAR in the amygdala and in the dorsal hippocampus, indicating limited plasticity. However, blocking b-adrenergic receptors before strong training caused memory to be formed as a mild one; it rendered memory susceptible to reconsolidation-blockade and restored GluA2 and NR2B levels towards those found in mildly trained rats. Together, these findings reveal that mild and strong fear memories are fundamentally different, with the latter showing a reduction in lability mechanisms and an inability to undergo reconsolidation. Importantly, b-adrenergic activity during fear learning is critical for these outcomes, revealing that noradrenaline shapes memory formation into a state that lacks lability.

Disclosures: **J. Haubrich:** None. **K. Nader:** None.

Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

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Presentation Number: 545.04

Topic: H.01. Animal Cognition and Behavior

Support: SAF2015-69767-P
MINECO/FEDER

Title: Activation of septal projections to CA1 interneurons promotes retrieval of contextual memory

Authors: A. SANS[1], A. RAZZAUTI[1], H. MONYER[2], ***C. SINDREU**[1];
[1]Univ. of Barcelona, Barcelona, Spain; [2]Clin. Neurobio. A230, Med. Fac. of Univ. Heidelberg & DKFZ, Heidelberg, Germany

Abstract: The CA1 output region of the hippocampus plays an essential role in the retrieval of episodic memories. GABAergic long-range projections from the medial septum (MS) densely innervate the hippocampus, but whether septal inputs regulate memory expression remains

elusive. Using viral-assisted circuit mapping in young adult mice of either sex, we found that MS to CA1 projections are recruited during recall of a contextual fear memory. Pharmacogenetic silencing of the MS-CA1 pathway impaired memory. Local inhibition of septal GABAergic terminals in CA1 also blocked memory. To clarify the microcircuit involved, we optogenetically activated septal GABAergic terminals and found that fast-spiking interneurons were preferentially inhibited. Anterograde viral transfer confirmed the abundance of parvalbumin-rich (PV+) cells. Thus, septal inputs may suppress PV+ cells in CA1 to allow for successful memory recall. To test the role of PV+ cells, we expressed the excitatory receptor hM3Dq in PV-cre mice. Direct activation of CA1 PV+ cells impaired memory, and prevented the stimulation of Erk/MAP kinase in postsynaptic pyramidal neurons. Our data indicate that suppression of feed-forward inhibition onto CA1 by septal GABAergic neurons is an important mechanism in gating contextual fear behavior.

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Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

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Presentation Number: 545.05

Topic: H.01. Animal Cognition and Behavior

Support: NARSAD YI
NIH NS047384

Title: A protein synthesis code for differential threat memory trace in central amygdala interneurons

Authors: *P. SHRESTHA[1], Z. SHAN[1], M. MAMCARZ[1], A. ZERIHOUN[1], C.-Y. JUAN[1], K. AGUSTIN[1], P. HERRERO VIDAL[1], N. HEINTZ[2], J. PELLETIER[3], E. KLANN[1];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]The Rockefeller Univ., New York, NY; [3]McGill Univ., Montreal, QC, Canada

Abstract: To survive in a dynamic environment, animals need to identify and appropriately respond to stimuli that signal danger. Species-specific defensive behaviors and autonomic responses are elicited upon encountering a stimulus predictive of threat. Pavlovian differential threat conditioning models associative learning that happens when animals learn to associate a previously neutral sensory stimulus e.g. an auditory tone paired with an aversive unconditioned stimulus e.g. a footshock and display defensive behaviors to the specific tone while resuming normal behavior during a safe tone. Centrolateral amygdala is a key brain region for processing and storing emotional memories. Consolidation of long term aversive memories requires *de novo* translation in the centrolateral amygdala (CeL). In this study, we used intersectional

chemogenetic strategies to block translation programs sensitive to levels of eukaryotic initiation factor 4E (eIF4E) and phosphorylated eukaryotic initiation factor 2α (p-eIF2α S51) in a temporally controlled, cell type-specific manner. Our first cell type-specific inducible protein synthesis inhibitor (ciPSI) strategy involves using the dual cre-loxP/tet-TRE system to knock down eIF4E using synthetic micro-RNA selective for eIF4E in specific cell types. Our second ciPSI strategy involves using a NS3/4 protease-sensitive drug-inducible kinase for eIF2α S51 with temporal precision. It is well known that cap-dependent translation is sensitive to levels of eIF4E, which forms part of the mRNA cap binding complex, whereas general translation is effectively blocked upon phosphorylation of eIF2α. Somatostatin interneurons (SOM IN) and Protein Kinase Cδ interneurons (PKCδ IN) are major GABAergic cell populations in the centrolateral amygdala that are engaged during emotional learning. Using our chemogenetic approaches, we find that both cap-dependent as well as general translation are required in CeL SOM interneurons for consolidation of long term threat memory and expression of appropriate defensive response to the paired tone. However, disruption of *de novo* translation in PKCδ interneurons selectively impaired discrimination of the safe tone leading to stimulus generalization. We further find that oxytocinergic modulation of PKCδ interneurons during differential threat learning is necessary for long-lasting discrimination of a threat-predictive tone from a safe tone. Our results suggest that elements of a differential threat memory are compartmentalized in distinct CeL interneuron populations and provide new mechanistic insight into the role of protein synthesis in consolidation of long term memories.

Disclosures: P. Shrestha: None. **Z. Shan:** None. **M. Mamcarz:** None. **A. Zerihoun:** None. **C. Juan:** None. **K. Agustin:** None. **P. Herrero Vidal:** None. **N. Heintz:** None. **J. Pelletier:** None. **E. Klann:** None.

Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

Location: Room N227

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 545.06

Topic: G.01. Appetitive and Aversive Learning

Support: Startup funds from the College of Agricultural and Life Sciences at Virginia Tech
Startup funds from the College of Sciences at Virginia Tech

Title: Sex-dependent differences in the engagement of the ubiquitin-proteasome system during fear memory formation

Authors: *T. J. JAROME[1], T. MCFADDEN[1], S. A. ORSI[2], J. L. NELSEN[3], M. O'DONNELL[3], N. JONES[3], R. K. DEVULAPALLI[3], E. L. MCCOIG[3], K. MARTIN[3];
[1]Animal and Poultry Sci., [2]Dept. of Biochem., [3]Sch. of Neurosci., Virginia Polytechnic Inst. and State Univ., Blacksburg, VA

Abstract: The formation of long-term fear memories requires increased transcriptional regulation and new protein synthesis in the amygdala (Bailey et al. 1999; Schafe & LeDoux 2000). Recently, strong evidence has emerged that protein degradation mediated by the ubiquitin-proteasome system is also critical for fear memory formation in the amygdala (Jarome & Helmstetter, 2013). However, studies implicating ubiquitin-proteasome signaling in memory formation have focused exclusively on male rodents, leaving questions about whether females share a similar requirement for this protein degradation process. Here, we found that while male and female rats had similar performance on a contextual fear conditioning task, they differed dramatically in their engagement of the ubiquitin-proteasome system in the amygdala. Consistent with our previous work (Orsi et al. 2019), male rats had increased overall and degradation-specific lysine-48 (K48) polyubiquitination and proteasome activity in the nucleus of amygdala cells 1 hr after fear conditioning. Surprisingly, females did not show any changes in K48 and overall polyubiquitination or proteasome activity in the nucleus following fear conditioning, nor did they in any other subcellular compartment, suggesting that they do not engage the ubiquitin-proteasome system in the amygdala during fear memory formation. Further analysis of naïve animals revealed that females had elevated baseline levels of overall and K48 protein polyubiquitination and proteasome activity in amygdala nuclei relative to males, which was associated with an increase in free (unconjugated) ubiquitin. Gene expression analyses identified that females had increased expression of the ubiquitin coding gene *Uba52*, but not *Ubb*, *Ubc* and *Rps27a*, suggesting that *Uba52* may be contributing to the elevated baseline levels of protein ubiquitination. Methylated DNA immunoprecipitation analysis revealed a significant increase in DNA 5-hydroxymethylation (5-hmc), an active transcriptional mark, in the promoter region of *Uba52* in female rats, suggesting that sex-dependent baseline differences in DNA 5-hmc may contribute to the different activity states of the ubiquitin-proteasome system. Collectively, these results suggest that males and females differ in their engagement of the ubiquitin-proteasome in the amygdala during fear memory formation, which may be due to DNA 5-hmc-mediated increases in transcription of *Uba52* at baseline. These results have important implications for understanding sex-different differences in the formation of fear-based memories that underlie a variety of psychiatric conditions such as post-traumatic stress disorder.

Disclosures: **T.J. Jarome:** None. **T. McFadden:** None. **S.A. Orsi:** None. **J.L. Nelsen:** None. **M. O'Donnell:** None. **N. Jones:** None. **R.K. Devulapalli:** None. **E.L. McCoig:** None. **K. Martin:** None.

Nanosymposium

545. Molecular Mechanisms of Memory Formation and Reconsolidation

Location: Room N227

Time: Tuesday, October 22, 2019, 1:00 PM - 2:45 PM

Presentation Number: 545.07

Topic: G.01. Appetitive and Aversive Learning

Support: 17K10286

Title: Selective agonists for delta-opioid receptor, KNT-127 and SNC80, differentially act on extinction learning of contextual fear memory in mice

Authors: *D. YAMADA[1], S. YANAGISAWA[1], S. YANAGITA[2], J.-I. OKA[1], H. NAGASE[3], A. SAITOH[1];
[1]Fac. of Pharmaceut. Sci., [2]Fac. of Sci. and Technol., Tokyo Univ. of Sci., Noda, Chiba, Japan; [3]IIIS, Univ. of Tsukuba, Tsukuba, Ibaraki, Japan

Abstract: In the present study, we evaluate the effects of KNT-127 and SNC80 on the contextual fear memory in the contextual fear conditioning test. Male C57BL/6J mice were used. On the conditioning day, the mice were trained with eight conditioning trials (0.8 mA x 1s, inter-trial interval 30 s). Twenty-four h following the conditioning, the mice were administered with drugs subcutaneously. After 30 min, the mice were re-exposed to the same context for 6 min (extinction training session). Twenty-four hours after the extinction, each mouse was placed in the conditioning chamber and a 6-min test was performed (memory testing session). During each session, no footshock was given, and the mouse's behavior was monitored every 1 min. In the extinction training session, KNT-127 and SNC80 significantly reduced freezing time in mice when compared with saline. In memory testing session, KNT-127 significantly reduced freezing time, while SNC80 treatment exhibited no significant effects. Further, the effects of KNT-127 were reversed by pretreatment with a DOP antagonist naltrindole. These results suggest that KNT-127 produced the anxiolytic-like effects in extinction training session and facilitated the extinction learning of contextual fear memory though the DOP. On the other hand, it was suggested that SNC80 produced the anxiolytic-like effects but produced no facilitating effects on extinction leaning. We proposed that KNT-127, but not SNC80, facilitates extinction learning of contextual fear memory via DOP in mice.

Disclosures: D. Yamada: None. **S. Yanagisawa:** None. **S. Yanagita:** None. **J. Oka:** None. **A. Saitoh:** None. **H. Nagase:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.01

Topic: H.02. Human Cognition and Behavior

Support: U01 DA041174
U01 DA041120
U01 DA041148
U24 DA041123

NSF 1714321

Title: Characterizing behavioral and neural signatures of working memory in childhood

Authors: *M. D. ROSENBERG[1,2], S. MARTINEZ[1], K. M. RAPUANO[1], M. I. CONLEY[1], A. O. COHEN[3], M. D. CORNEJO[4], D. J. HAGLER, Jr.[4], K. M. ANDERSON[1], T. D. WAGER[5], E. J. FECZKO[6], E. EARL[6], D. A. FAIR[6], D. M. BARCH[7], R. WATTS[1], B. J. CASEY[1];
[1]Yale Univ., New Haven, CT; [2]Univ. of Chicago, Chicago, IL; [3]New York Univ., New York, NY; [4]Univ. of California San Diego, San Diego, CA; [5]Univ. of Colorado Boulder, Boulder, CO; [6]Oregon Hlth. & Sci. Univ., Portland, OR; [7]Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Working memory function changes across development and varies across individuals. The patterns of behavior and brain function that track individual differences in working memory during development, however, are not well understood. To establish associations between working memory, other cognitive and attentional abilities, and functional MRI activation in childhood, we analyze data from over 4,000 9-10-year-olds enrolled in the Adolescent Brain Cognitive Development study, an ongoing longitudinal study in the United States. Behavioral analyses reveal robust relationships between working memory, short-term memory, language skills, and fluid intelligence. Analyses relating out-of scanner working memory performance to memory-related fMRI activation in an emotional *n*-back task demonstrate that frontoparietal activity in response to an explicit memory challenge indexes working memory ability. Furthermore, this relationship is domain-specific, such that fMRI activation related to emotion processing during the emotional *n*-back task, inhibitory control during a stop-signal task, and reward processing during a monetary incentive delay task does not track memory abilities. Together these results inform our understanding of the emergence of individual differences in working memory and lay the groundwork for characterizing the ways in which they change across adolescence.

Disclosures: **M.D. Rosenberg:** None. **S. Martinez:** None. **K.M. Rapuano:** None. **M.I. Conley:** None. **A.O. Cohen:** None. **M.D. Cornejo:** None. **D.J. Hagler:** None. **K.M. Anderson:** None. **T.D. Wager:** None. **E.J. Feczko:** None. **E. Earl:** None. **D.A. Fair:** None. **D.M. Barch:** None. **R. Watts:** None. **B.J. Casey:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.02

Topic: H.02. Human Cognition and Behavior

Support: NIMH grant 5R01-MH087214
Office of Naval Research grant N00014-12-1-0972

National Institute of Mental Health grant 5T32-MH020002
TKF Foundation
National Science Foundation BCS-1632445
John Templeton Foundation

Title: Distinguishing cognitive effort and working memory load

Authors: *O. KARDAN[1], K. C. S. ADAM[2], I. MANCE[3], N. W. CHURCHILL[4], E. K. VOGEL[1], M. G. BERMAN[1];
[1]Psychology, The Univ. of Chicago, Chicago, IL; [2]Univ. of California San Diego, San Diego, CA; [3]Univ. of Oregon, Eugene, OR; [4]St. Michael's Hosp., Toronto, ON, Canada

Abstract: Despite being intuitive, cognitive effort has proven difficult to quantify, with some researchers equating it with working memory (WM) load and others seeing the two as separate constraints on the cognitive system. Recent research has shown that suppression of scale-invariance (*H*) of brain activity measured by fMRI could delineate exertion of higher levels of cognitive effort. In the current study we validated the correspondence between scale-invariance (*H*) of cortical activity recorded by EEG, a much higher frequency signal, and WM task load during two WM experiments with varying set sizes. We used this neural signature to disentangle cognitive effort from the number of items in WM by investigating *H* suppression beyond WM capacity. Our results showed monotonic decreases in *H* with increased set size, even after set size exceeded WM capacity. This behavior of *H* contrasted with behavioral performance and an oscillatory indicator of WM load (i.e., alpha-band desynchronization), both of which showed a plateau at difficulty levels surpassing WM capacity. This is the first reported evidence for the suppression of scale-invariance in EEG due to task difficulty, and our work suggest that *H* suppression may be used to quantify changes in effort even when working memory load is constant and at maximum capacity.

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Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.03

Topic: H.02. Human Cognition and Behavior

Support: NIMH R56MH115042 (to T.J.B)
ONR N000141410681 (to T.J.B)
NDSEG Fellowship (to M.F.P)

Title: Neural mechanisms of retrospective selection in visual working memory

Authors: *M. F. PANICHELLO, T. J. BUSCHMAN;
Princeton Neurosci. Inst., Princeton, NJ

Abstract: Working memory has a severely limited capacity. Humans and other animals compensate for this processing bottleneck by allocating working memory resources in accordance with their goals. This prioritization process is not limited to selectively encoding certain items into working memory. Rather, even as information is maintained in working memory, subsets of items can be enhanced at the expense of others. However, neither the neural mechanisms underlying this retrospective selection nor its relation to better-studied forms of prospective selection (e.g., visuospatial attention) are well understood.
To explore these questions, we trained two macaque monkeys to switch between a retrospective and prospective selection task. Both tasks had the same basic structure: animals were presented with one or two colored squares (the "samples") at different locations on a screen. After a memory delay, the animal reported one of the two items on a continuous scale. Critically, a spatial cue indicating which item was task relevant either appeared before (prospective) or after (retrospective) the samples. Behavioral analyses indicate that this cue manipulation led the animal to adopt a retrospective or prospective selection strategy. Report precision decreased with load on retrospective trials but not prospective trials, suggesting that the animals encoded only the cued sample on prospective trials. Report accuracy increased when retrospective cues appeared earlier during the delay on two-item trials, suggesting that the animals prioritized one item in memory to prevent decay. To understand the neural mechanisms supporting attention and selection, we simultaneously recorded neural activity in prefrontal and parietal regions associated with attentional control. The neural representations of the locus of attention during prospective and retrospective trials overlapped both at the single neuron and the population level. Furthermore, both prospective and retrospective cues enhanced information about the cued color in prefrontal cortex. These results suggest that overlapping mechanisms underlie retrospective and prospective selection.

Disclosures: M.F. Panichello: None. **T.J. Buschman:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.04

Topic: H.02. Human Cognition and Behavior

Support: 17ZDA323
16PJC022

Title: The dissociation of covert spatial attention during visual working memory

Authors: *S. HAN, Y. KU;
East China Normal Univ., Shanghai, China

Abstract: Covert spatial attention can be divided into endogenous attention and exogenous attention. It is well known that these two types of attention exert their functions distinctively in perceptual field. However, whether such dissociation appears in working memory field remains unclear yet. To address this issue, we conducted 4 experiments (*N*=132, 50 males, aged 18-28) using the retro-cue paradigm in combination with the StandardMixture Model and neuroimaging techniques. The general design was that one of 2 or 4 gabors in memory display would be cued either by an endogenous cue or by an exogenous cue during the middle of delay and then probed at the test phase. These retro-cue trials were randomly mixed with no cue trials, serving as a baseline. In experiment 1 (*N*=64, 21 males) and 2 (*N*=20, 6 males), pupillary responses and EEG were recorded respectively. We consistently found that both retro-cues similarly enhanced precision under load-4, while exogenous cues led to larger retro-cue benefits than endogenous cues by decreasing the guess rate under load-2. This distinction could be explained by a larger pupil changes as well as a shorter latency of anterior directing attention negativity (ADAN) during 300-500ms after the exogenous cue onset. To determine the critical brain areas where retro-cues were processed and how memory representation was changed over time, we conducted a MEG study (*N*=27, 14 males) combined with Multivariate Pattern Analysis (MVPA) and Granger Causality Analysis (GCA). The behavioral pattern duplicated the above results and we additionally found that a stronger activation at left prefrontal cortex (LPFC) for exogenous cues than endogenous cues during the post-cue 300-500ms could positively predict their behavioral differences. MVPA results further indicated that exogenous cues maintained the target representation throughout the whole post-cue period. GCA results confirmed this by showing that the top-down control from LPFC to lateral occipital cortex (LOC) started within 0-200ms after the exogenous cue onset. To examine the causal role of LPFC in retro-cue processing, we conducted a TMS study (*N*=21, 9 males). We found that a single pulse at LPFC could eliminate the retro-cue benefits by exogenous cues alone when the stimulation was given at post-cue 100ms. Together, these findings suggested a lower level of internal noise as well as a faster and stronger LPFC activation induced by exogenous than endogenous retro-cues under the low load. The present findings may shed light on the interplay between attention and working memory and further reveal the differentiation between perceptual attention and mnemonic attention.

Disclosures: S. Han: None. **Y. Ku:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.05

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1U19NS107609
NIH Grant R37NS21135
NIH Grant 1K99MH120048

Title: Event segmentation reveals working memory forgetting rate

Authors: *A. JAFARPOUR[1], E. A. BUFFALO[2], R. T. KNIGHT[3], A. G. COLLINS[3]; [2]Physiol. and Biophysics, [1]Univ. of Washington, Seattle, WA; [3]Univ. of California Berkeley, Berkeley, CA

Abstract: We perceive the world as a series of events and fluidly segment them into episodes. Although there is general agreement on the segmentation at the occurrence of a salient event, the number of determined segments is variable across individuals. Working memory plays a key role in tracking and segmenting a sequence of events; however, it is unclear which aspect of working memory is related to individual variability in event segmentation. We used computational modeling to extract the working memory capacity and forgetting rate of healthy adults (n=36) from an association learning task. We then assessed the relationship between individuals' working memory limitations and the subjective number of determined events in three movies with different storylines. We found that memory decay, measured in the learning task, is related to event segmentation: Participants who perceived either a very low (under-segmenters) or a very high (over-segmenters) number of events had a higher forgetting rate. We observed that under-segmenters performed better on a temporal recognition task for the movie with a linear storyline and an overarching story, benefiting from the schema. In contrast, the over-segmenters performed better at free recall than under-segmenters for all the movies. The results provide evidence that variability in forgetting rate is linked to the variability in event perception. This research was supported by the National Institute of Neurological Disorders and Stroke 1U19NS107609 (E.A.B.) and R37NS21135 (R.T.K.) and the National Institute of Mental Health 1K99MH120048 (A.J.).

Disclosures: A. Jafarpour: None. **E.A. Buffalo:** None. **R.T. Knight:** None. **A.G. Collins:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.06

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant GR035189
NSF Grant GR027296

Title: Whole-brain functional connectivity predicts working memory performance in novel healthy and memory-impaired individuals

Authors: *E. W. AVERY[1], K. R. YOO[1], M. D. ROSENBERG[1], Y. KWON[1], A. S. GREENE[2], S. GAO[3], D. L. NA[7], D. SCHEINOST[4], R. T. CONSTABLE[2,4,5], M. M. CHUN[1,2,6];
[1]Dept. of Psychology, [2]Interdept. Neurosci. Program, [3]Dept. of Biomed. Engin., [4]Dept. of Diagnos. Radiology, [5]Dept. of Neurosurg., [6]Dept. of Neurosci., Yale Univ., New Haven, CT; [7]Dept. of Neurol., Sungkyunkwan Univ. Sch. of Med., Seoul, Korea, Republic of

Abstract: Critical to navigating everyday life, working memory (WM), fluid intelligence (gF), and attention are among the most heavily researched topics in neuroscience. However, the neural bases of individual differences in these cognitive abilities and the interactions between them remain poorly understood. Using a data-driven technique known as connectome-based predictive modeling (Finn et al., 2015; Rosenberg et al., 2016a; Shen et al., 2017), we built models to predict individual WM from whole-brain functional connectivity patterns measured with fMRI. When defined using *n*-back or rest data from the Human Connectome Project (HCP), connectome-based models significantly predicted novel individuals' 2-back accuracy (n = 502; mean age 28±3.6; correlation between predicted/observed scores: task: r=0.36, p<0.001; rest: r=0.20, p<0.001; Avery et al., 2018). Model predictions also correlated with gF (Penn's Progressive Matrices: r=0.28, p<0.001) but did not significantly correlate with sustained attention (Short Penn Continuous Performance: r=0.09, p=7.2*10^{-2}). Models trained to predict gF also predicted WM (r=0.34, p<0.001), while sustained attention models again did not (r=0.16, p=6.4*10^{-2}). This pattern of results reflects the documented, strong relationship between WM and gF (Colom et al., 2002, 2004) and weaker relationship between WM and sustained attention (Barrett et al., 2004). Anatomical feature analysis revealed significant overlap between WM and gF models, particularly in utilization of prefrontal and parietal regions, and less overlap between WM and attention models. Furthermore, demonstrating external validity, the WM model generalized to predict memory performance in the Rey Complex Figure Test and Seoul Verbal Learning Task in an independent dataset of 157 older adults recruited from Samsung Medical Center in Korea (mean age 68.7±9.6; 48 healthy, 54 amnestic mild cognitive impairment, 55 Alzheimer's disease; r=0.37, p<0.001). The HCP-developed attention model, too, generalized in an independent external validation, predicting individual attention performance in a gradual-onset continuous performance task in a dataset of 76 young adults collected at Yale University (mean age 22.9±4.6; r=0.35, p<0.001). Our results suggest that data-driven predictive modeling approaches can elucidate independent components of WM, gF, and attention, revealing distinct networks supporting WM and attention.

Disclosures: E.W. Avery: None. **K.R. Yoo:** None. **M.D. Rosenberg:** None. **Y. Kwon:** None. **A.S. Greene:** None. **S. Gao:** None. **D.L. Na:** None. **D. Scheinost:** None. **R.T. Constable:** None. **M.M. Chun:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.07

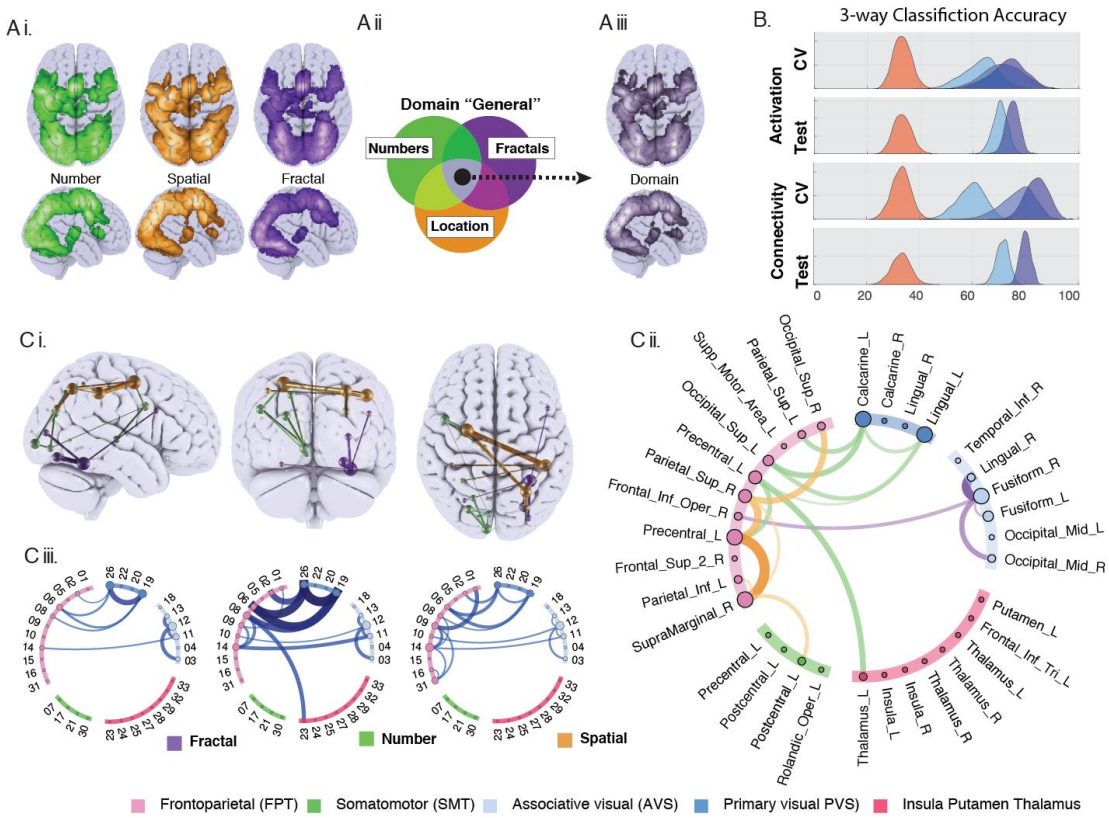
Topic: H.02. Human Cognition and Behavior

Support: MRC project grant MR/R005370/1

Title: Dynamic network coding of working-memory domains and working-memory processes

Authors: *E. S. SOREQ, A. HAMPSHIRE;
Imperial Col. London, London, United Kingdom

Abstract: Contemporary network science implies that working memory (WM), among other cognitive processes, relies upon a dynamic distributed network in the brain. Here we present evidence from our recent publication together with additional findings demonstrating how transient patterns of brain connectivity and activity code for distinct aspects of WM processes. Specifically, we show (see A iii) how seemingly uniform "non-specific" activity in the "multiple demands cortex", a central system in the brain linked with cognitive taxing engagement can be easily fragmented to localised nodes and that these nodes are sensitive enough to differentiate between canonical WM domains. We further show how pairwise dynamic functional connectivity across these nodes also contains generalised WM domain-specific patterns. Using an advanced suite of machine-learning methods together with exhaustive random sampling and an independent replication study, we demonstrate that WM domains (spatial, pattern and number) and processing stages (encode, maintain, retrieve) are classifiable with high accuracy from these patterns (see B). Contrary to early neuropsychological perspectives, these aspects of WM do not map exclusively to specific brain areas, processing streams or connections (see C). However, we identified prominent features within the multivariate connectivity patterns corresponding with previously reported mappings from that literature. Furthermore, connectivity patterns provide the most precise basis for classification and become fine-tuned as maintenance load increases. These results accord with a network-coding mechanism, where the same brain regions support diverse WM demands by adopting different connectivity states.



Disclosures: **E.S. Soreq:** None. **A. Hampshire:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.08

Topic: H.02. Human Cognition and Behavior

Support: NEI R01-EY025872
James S McDonnell Foundation Scholar Award
Marie Sklodowska-Curie Grant Agreement No 743941
Institute for Neural Computation Predoctoral Fellowship (NIMH)

Title: Complementary strategies for encoding information in working memory

Authors: *M. M. HENDERSON[1], R. L. RADEMAKER[2], J. T. SERENCES[2];
[1]Neurosciences Grad. Program, [2]Psychology, UCSD, La Jolla, CA

Abstract: Working memory (WM) allows observers to hold information in mind to guide future behavior. In some cases, information is stored in a format that resembles stimulus-driven responses in early visual areas so that the details of an object can later be distinguished from similar items. In other cases, it is advantageous to use a more high-level coding scheme. For example, instead of remembering the visual details of your route to work, you could remember a series of planned motor commands. Here, we used fMRI and multivariate encoding and decoding analyses to compare information about remembered features under conditions encouraging sensory-like or motor-like strategies. Subjects remembered the orientation of a briefly (500 ms) presented grating over a fixed delay (12 sec). Next, a spinning dial was shown, rotating at a fixed speed for 3s. Subjects pressed a button when the dial matched the remembered orientation; no feedback was given. We manipulated the predictability of the dial *starting position* and *rotation direction*. On trials where both were known beforehand, subjects could plan their motor response as soon as the grating appeared, while on trials where one or both were unknown, subjects needed to maintain the precise orientation until the end of the delay period. In early retinotopic visual areas, we found that while we were able to recover a representation of the memory stimulus during the delay period of all conditions, representation fidelity was significantly worse during the fully predictable condition, suggesting that early sensory areas were relied upon less when the motor response could be planned ahead of time. Conversely, in the intraparietal sulcus and in primary motor cortex, we found more information about the target orientation during the fully predictable condition compared to other conditions. This effect developed gradually along the posterior-anterior axis of the brain. Overall, these findings demonstrate that the brain can employ multiple complementary strategies for encoding information that are not mutually exclusive. This may help to reconcile apparently disparate findings about the role of early visual areas in human and non-human primate studies of WM.

Disclosures: M.M. Henderson: None. **R.L. Rademaker:** None. **J.T. Serences:** None.

Nanosymposium

546. Working Memory: Mechanisms II

Location: Room S402

Time: Tuesday, October 22, 2019, 1:00 PM - 3:15 PM

Presentation Number: 546.09

Topic: H.02. Human Cognition and Behavior

Support: ERC StG Agreement 313658

Title: Shared resources between visual attention and visual working memory are allocated through rhythmic sampling

Authors: *E. BALESTRIERI[1], L. RONCONI[2], D. MELCHER[3];
[1]Univ. of Muenster, Muenster, Germany; [2]Univ. Vita-Salute San Raffaele, Milan, Italy; [3]Univ. of Trento, Rovereto, Italy

Abstract: The relationship between attention and working memory remains a fundamental question in neuroscience. We investigated whether these two processes share a common resource by capitalizing on a recent set of studies showing that attention is intrinsically rhythmic, oscillating over time. Using a dual-task approach, we combined a classic VWM task with a detection task in which we densely sampled detection performance during the time between the memory and the test array. Consistent with a shared resource, an increment in VWM load led to impaired detection of near threshold visual stimuli. Moreover, the highest VWM load condition also led to the presence of an oscillatory pattern in detection performance at ~5 Hz (see Figure 1). The frequency of this attention sampling rhythm changed according to the strategic allocation of attentional resources to either the VWM or the detection task (see Figure 2). This pattern of results is consistent with a central sampling attentional rhythm which allocates shared attentional resources both to the flow of external visual stimulation and also to the internal maintenance of visual information.

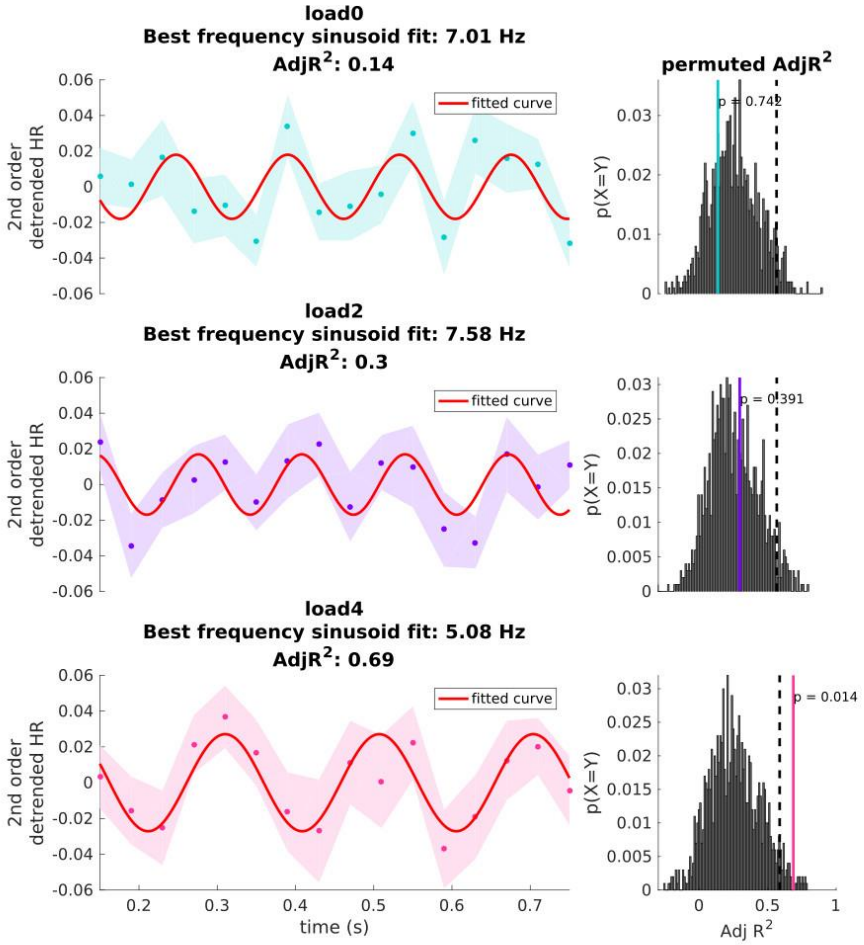


Figure 1: Average of HR time series after detrend with related sinusoidal fitting.

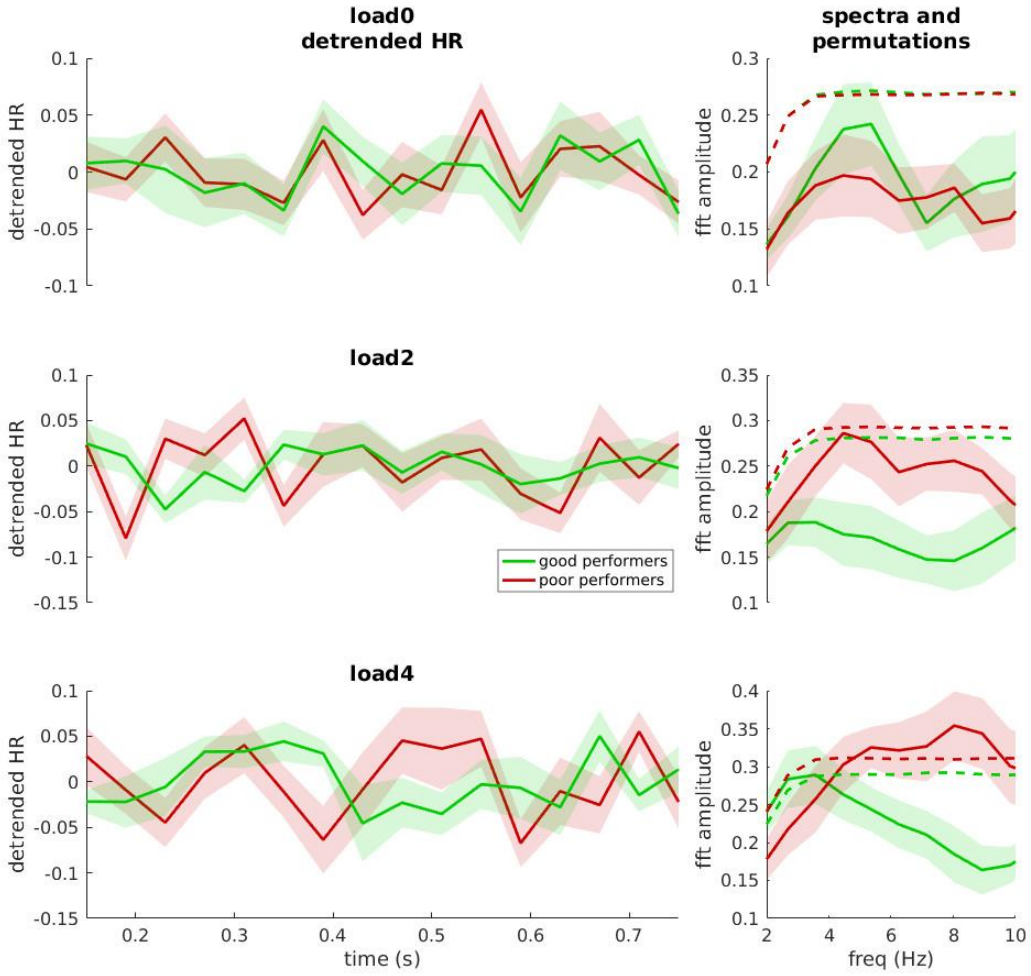


Figure 2: HR time series after detrend for “good” and “poor” performers in VWM, and average of corresponding spectra of HR time series.

Disclosures: **E. Balestrieri:** None. **L. Ronconi:** None. **D. Melcher:** None.

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

Location: Room S106

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 547.01

Topic: I.04. Physiological Methods

Support: Howard Hughes Medical Institute

Title: All optical functional screens for directed evolution of protein based biosensors

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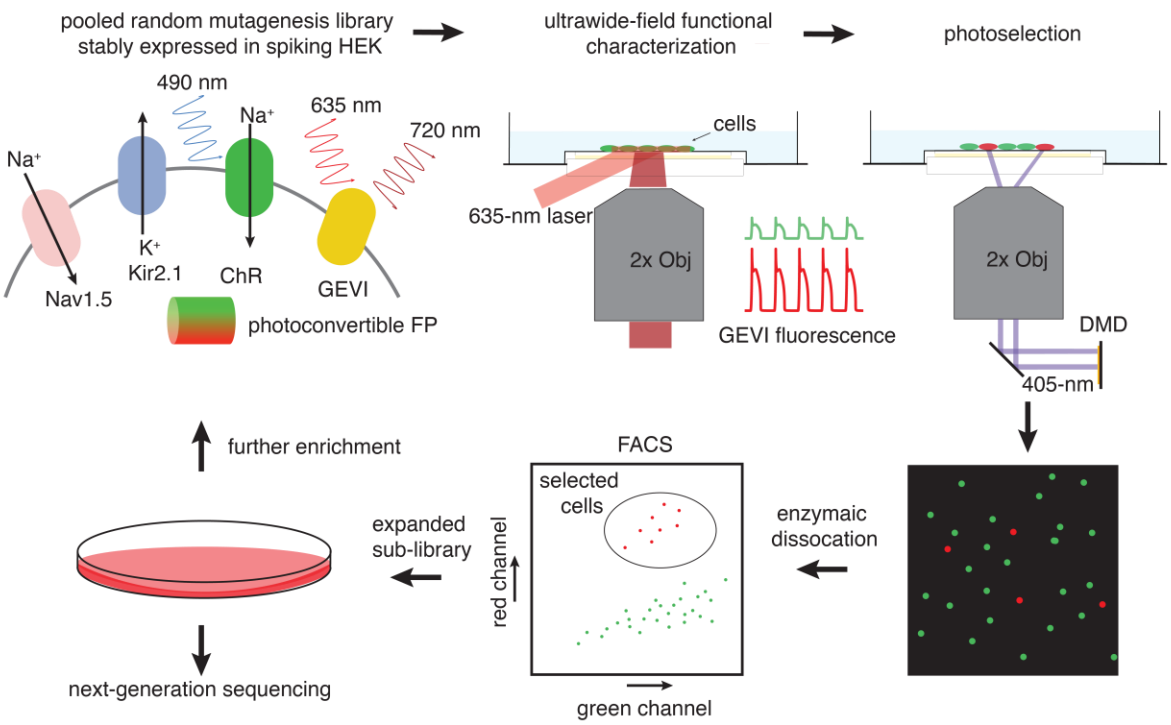
Abstract: Genetically encoded fluorescent biosensors are a powerful tool for investigating biological signaling. These tools have been particularly important in neuroscience, where e.g. sensors of Ca^{2+} and membrane voltage enable imaging of neural dynamics *in vivo*. Developing such biosensors often requires extensive optimization and screening. However, classic strategies for screening proteins, such as fluorescence- activated cell sorting or surface display techniques, fall short when dynamic parameters matter. Plate-based assays where one mutant is expressed per well have limited throughput. Here we develop a general-purpose platform for directed evolution of biosensors based on their dynamic properties. Starting with a pooled library of mutant sensors, we express one copy per cell in a mammalian cell line. We co-express the mutants with a photo-switchable fluorescent protein. We then trigger sensor activation, monitor the response of thousands of cells in parallel using an ultra wide-field fluorescence microscope, and photoconvert the switchable tag in the cells expressing mutants that show favorable responses. We then use FACS sorting and high-throughput sequencing to identify the promising mutants. We apply this screening platform to improve a red-shifted archaerhodopsin-derived genetically encoded voltage indicator (GEVI). The pooled GEVI variant library is expressed in spiking HEK cells, which can be triggered via a flash of blue light to produce action potentials. After three rounds of enrichment, we analyze the frequency shift of genetic mutations from the original to the final library to identify desirable mutations. This procedure led to GEVIs with substantially improved performance. We envision that the improved GEVIs will expand our ability to optically probe neural circuits and other electrically active cells. Furthermore, the screening platform will prove a powerful tool for engineering other biosensors.



Disclosures: **H. Tian:** None. **B. Gmeiner:** None. **V. Parot:** None. **H. Dahche:** None. **S. Begum:** None. **K. Williams:** None. **T. Green:** None. **H. Xu:** None. **A.E. Cohen:** A. Employment/Salary (full or part-time):; Howard Hughes Medical Institute. Other; AEC is a founder of Q-state Biosciences.

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

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Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 547.02

Topic: I.04. Physiological Methods

Support: NIH CEBRA
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DARPA

Title: Near infrared optical probes enable dopamine imaging with high spatiotemporal resolution

Authors: ***A. G. BEYENE**[1], K. DELEVICH[1], J. T. DEL BONIS-O'DONNELL[1], D. PIEKARSKI[3], W. LIN[4], A. W. THOMAS[1], S. J. YANG[1], P. KOSILLO[1], D. YANG[1], L. E.

WILBRECHT[2], M. P. LANDRY[5];
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Abstract: Dopamine plays critical roles in sculpting the operating modes of local neuronal circuits that drive complex behavioral outcomes, including learning and motivation. As a consequence, dopamine plays important roles in reward motivated behavior, and is implicated in a wide range of neurological and psychiatric disorders. However, tools to measure dopamine dynamics with high spatial and temporal fidelity have been lacking, limiting our ability to investigate dopamine dynamics. In this work, we describe the design and use of a nanoscale turn-on near-infrared (NIR) fluorescent reporter that captures transients in dopamine levels in striatal brain tissue with high spatial resolution.[1] This NIR catecholamine imaging probe (NIRCat) is based on functionalized, non-photobleaching carbon nanostructures that emit in the NIR at 1000-1300 nm. In the dorsal striatum, NIRCat can report dopamine transients driven by single pulse electrical or optogenetic stimulation. Importantly, NIRCat probe dopamine through synthetic molecular recognition sites. These recognition motifs enable NIRCat to exhibit unperturbed functionality in the presence of dopamine receptor agonists and antagonists, enabling micron-scale imaging of previously undetected heterogeneities in D2 autoreceptor modulation of presynaptic dopamine release. Our results suggest NIRCats may uniquely support similar explorations of processes that regulate dopamine neuromodulation at the level of individual synapses, and exploration of the effects of receptor agonists and antagonists that are commonly used as psychiatric drugs.
1. Imaging Striatal Dopamine Release Using a Non-Genetically Encoded Near-Infrared Fluorescent Catecholamine Nanosensor. Science Advances (2019).

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Topic: I.04. Physiological Methods

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Title: Comparative performance of a bacterial phytochrome and an opsin-based GEVI in intact brain tissue

Authors: *C. SONG[1], M. MATLASHOV[2], M. MONAKHOV[2], V. VERKHUSHA[2], T. KNOPFEL[1];
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Abstract: Genetically encoded voltage indicators (GEVIs) with fluorescence excitation and emission in the near-infrared (NIR) spectrum (> 600 nm) hold great potential for combination of voltage imaging with blue light-controlled optogenetic actuation. We previously reported the development of a NIR GEVI using bright near-infrared fluorescent proteins from bacterial phytochromes (https://doi.org/10.1101/536359). This NIR GEVI variant reliably reports neuronal activities including subthreshold membrane potential depolarization and hyperpolarization, as well as spontaneous spiking, or electrically- and optogenetically-evoked action potentials in neuronal cultures. This enables, in principle, largely improved all-optical causal interrogations of physiology. Here we tested the performance of this NIR GEVI in intact brain tissue in comparison with the opsin-based GEVI Archon1. Neuronal cultures transduced with AAV1.CaMK-NIR GEVI displayed 5-fold higher brightness as compared to those transduced with AAV1.CaMK-Archon1. We then imaged acute brain slices prepared from animals up to 5 weeks after injection of AAV1.CaMK-NIR GEVI or AAV1.CaMK-Archon1. Optical population responses were induced by electric stimulations (1 pulse, 5 pulses at 20Hz, and 5 pulses at 100Hz) and recorded with either photodiodes or cameras. Responses in the hippocampus of Archon1-expressing slices had an approximately 2-fold larger $\Delta F/F$ values than those expressing NIR GEVI (for single pulse stimulation: range 0.36 to 1.50% vs 0.18 to 0.51% respectively), similar across different detectors. Electric stimulation-induced population responses were fitted with a double exponential decay curve. Fast optical signal decay time constants for 1 pulse and 5 pulses stimulation respectively were 12.7 ms and 10.7 ms for NIR GEVI, and 50 ms and 29 ms for Archon1. The relatively slower decay of Archon1 responses is unexpected given the reported fast kinetics of Archon1.

Disclosures: C. Song: None. **M. Matlashov:** None. **M. Monakhov:** None. **V. Verkhusha:** None. **T. Knopfel:** None.

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

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Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 547.04

Topic: I.04. Physiological Methods

Support: HHMI

Title: Designing genetically encoded voltage indicators for *in vivo* imaging

Authors: *A. S. ABDELFATTAH[1], R. VALENTI[1], T. KAWASHIMA[1], A. SINGH[1], O. NOVÁK[2], H. LIU[1], Y. SHUAI[3], Y.-C. HUANG[4], B.-J. LIN[4], R. PATEL[1], J. MACKLIN[5], T.-W. CHEN[4], G. C. TURNER[5], Z. LIU[1], M. KOYAMA[1], K. SVOBODA[6], M. B. AHRENS[1], L. D. LAVIS[1], E. R. SCHREITER[1];
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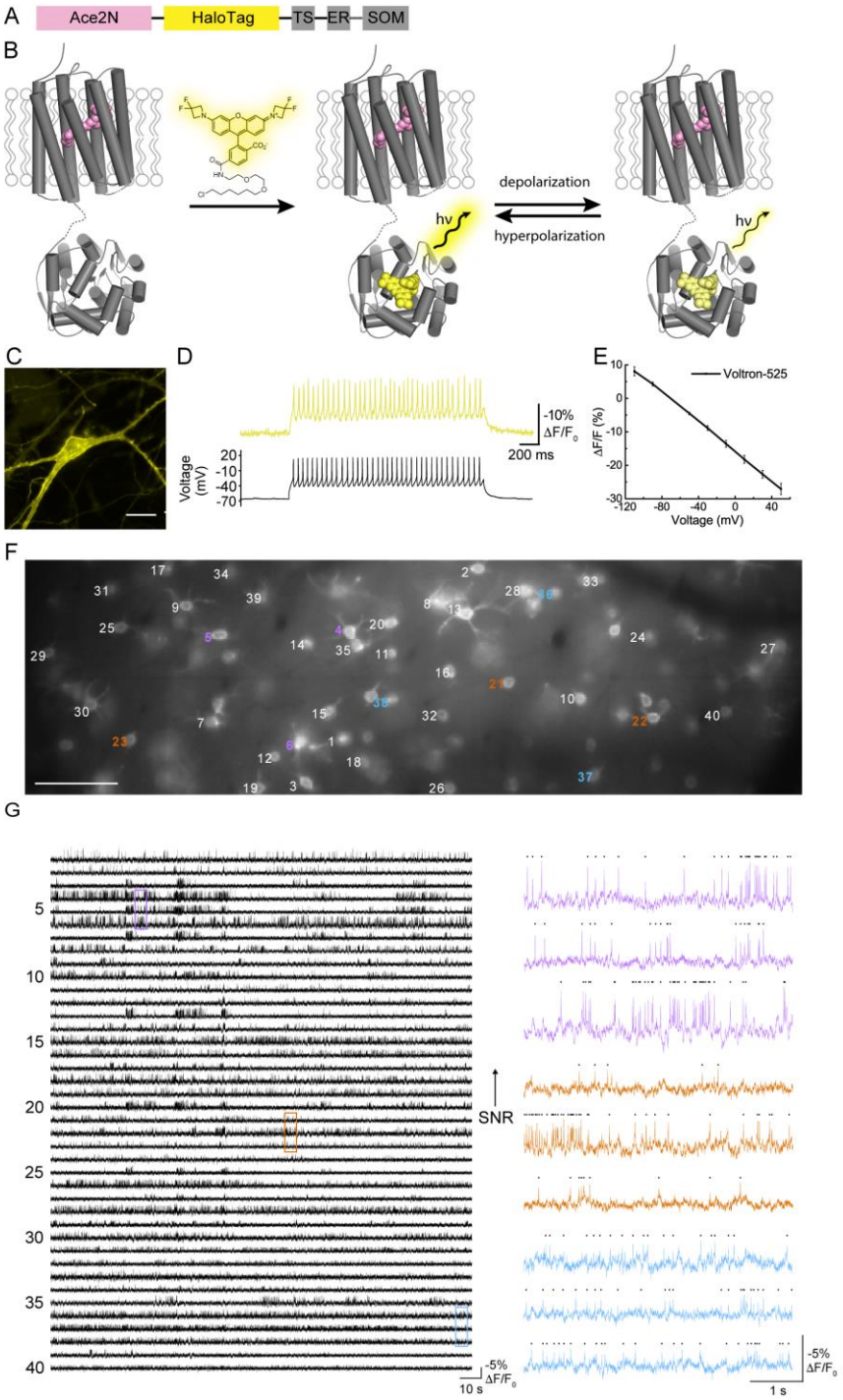
Abstract: Voltage imaging *in vivo* provides unparalleled spatial and temporal resolution of electrical signaling at the cellular and circuit levels. A longstanding challenge has been to develop genetically encoded voltage indicator proteins (GEVIs). Current GEVI designs use fluorescent proteins or rhodopsins as the reporting fluorophore. However, the intrinsic brightness and photostability of these fluorophores limits their utility *in vivo*. To address this issue, we engineered a GEVI, called Voltron, that utilizes bright and photostable dyes together with self-labeling protein tags. In Voltron, a self-labeling protein tag is fused to a rhodopsin voltage sensor domain (Fig. 1A-B). Voltage is reported as a fluorescence changes that arises from energy transfer (FRET) between the dye emission and rhodopsin absorption (Fig. 1B-E). Voltron is significantly brighter and more photostable than existing GEVIs, extending productive imaging time by more than 10 times in awake behaving mice (Fig. 1F-G), larval zebrafish, and fruit flies. Moreover, we describe detailed mechanistic insights into rhodopsin response to voltage changes that we discover using directed protein evolution and electrophysiology recordings. These mechanistic insights allow us to engineer improved Voltron and rhodopsin based GEVIs. Additionally, they allow us to rationally control the fluorescence response of the broad class of rhodopsin-based GEVIs to voltage changes in cells.
Fig. 1 (A-B) Schematic of Voltron sequence and function (C) Hippocampal neuron expressing Voltron labeled with JF-525 (D) Single-trial recording of action potentials using Voltron (E) Voltron fluorescence change as a function of membrane voltage. (F) Mouse visual cortex expressing Cre-dependent soma targeted Voltron (G) Left: Raw intensity traces from neurons labelled in E. Scalebars: 50% ΔF/F, 20s. Right: Zoom in on colored squares from ΔF/F traces on left.



Disclosures: **A.S. Abdelfattah:** None. **R. Valenti:** None. **T. Kawashima:** None. **A. Singh:** None. **O. Novák:** None. **H. Liu:** None. **Y. Shuai:** None. **Y. Huang:** None. **B. Lin:** None. **R. Patel:** None. **J. Macklin:** None. **T. Chen:** None. **G.C. Turner:** None. **Z. Liu:** None. **M. Koyama:** None. **K. Svoboda:** None. **M.B. Ahrens:** None. **L.D. Lavis:** None. **E.R. Schreiter:** None.

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Topic: I.04. Physiological Methods

Support: California National Primate Research Center Pilot Research Program

Title: Head mounted microendoscopic calcium imaging in deep layer premotor cortex of behaving rhesus macaque

Authors: A. BOLLIMUNTA[1], S. R. SANTACRUZ[2], R. W. EATON[3], P. S. XU[1], J. H. MORRISON[3], K. A. MOXON[3], J. M. CARMENA[4], ***J. J. NASSI**[1];
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Abstract: A major effort is now underway across the brain sciences to identify, characterize and manipulate mesoscale neural circuits in order to elucidate the mechanisms underlying sensory perception, cognition and motor behavior. Optical imaging technologies, coupled with genetically encoded calcium indicators (e.g. GCaMP), serve as an important tool toward these goals, allowing access to large-scale genetically defined neuronal populations in rodents. In particular, one photon miniature microscopes coupled with microendoscope GRIN lenses enable unprecedented readout of neural circuit dynamics in deep brain regions during active behavior. This has already led to breakthrough discoveries across a wide array of rodent brain regions and behaviors. However, in order to study the neural circuit mechanisms underlying more complex and clinically-relevant human behaviors, it is crucial to translate this technology to non-human primates. Here, we describe the first successful application of this technology to rhesus macaque, recording cellular-resolution calcium dynamics from neurons in deep layers of premotor cortex during naturalistic motor behavior. As part of this work we have identified a viral strategy for robust expression of GCaMP, an optimized surgical protocol for microendoscope GRIN lens insertion, and a chronic cranial chamber and lens mounting system for plug-n-play imaging in deep layers of gyral cortex. We show that the recorded calcium dynamics can be used to decode the animal's motor behaviors and that the relationship between individual neurons and behavior can be tracked longitudinally over time. Head-mounted microendoscopic calcium imaging in macaque promises to greatly advance our understanding of human brain function, as well as its dysfunction in neurological and neuropsychiatric disease.

Disclosures: **A. Bollimunta:** A. Employment/Salary (full or part-time):; Inscopix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix, Inc.. **S.R. Santacruz:** None. **R.W. Eaton:** None. **P.S. Xu:** A. Employment/Salary (full or part-time):; Inscopix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding

diversified mutual funds); Inscopix, Inc.. **J.H. Morrison:** None. **K.A. Moxon:** None. **J.M. Carmena:** None. **J.J. Nassi:** A. Employment/Salary (full or part-time):; Inscopix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix, Inc..

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

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Presentation Number: 547.06

Topic: I.04. Physiological Methods

Support: U01MH114824

Title: Super resolution oblique light sheet microscopy

Authors: *J. MIZRACHI[1], A. NARASIMHAN[2], X. QI[2], K. UMADEVI VENKATARAJU[3], D. ALBEANU[2], P. OSTEN[2];
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Abstract: The ability to examine the brain at the mesoscale whole-brain and nanometer scale local level is instrumental to understanding how brain structure gives rise to sensory, motor, and cognitive functions. Visualization of nanometer-scale structures, such as synapse density and distribution, provides deeper understanding of normal brain function and has the potential to reveal structural underpinnings of neuropsychiatric disorders. Large scale and nanometer scale structures can be studied separately, but we lack methodologies that could provide whole brain volumetric imaging, neural tracing, and 3D super-resolution imaging of a mammalian brain simultaneously. We introduce Super Resolution Oblique Light Sheet Microscopy (SR-OLST), an original technique that combines oblique light-sheet tomography (OLST), which we developed to image entire mouse brains at light-resolution level, and super-resolution light sheet microscopy for the examination of synapses with nanometer scale resolution in selected brain areas. The method comprises an automated combination of light sheet fluorescence microscopy (LSFM), vibratome sectioning, pixel-wise 3D deconvolution, custom image reconstruction software, original protocols for tissue clearing and buffers, and super-resolution optical fluctuation imaging (SOFI). We demonstrate super-resolution imaging of 100um^{3}volumes with 40x40nm pixel size, acquired in conjunction with whole mouse brain imaging at 0.4x0.4x1um pixel size. Imaging time for a whole mouse brain including a super-resolved region of interest is ~20 hours. Our device, techniques, and software comprise the first instrument capable of high speed generation of volumetric whole brain images and 3D super-resolution images simultaneously for the same mouse brain.

Disclosures: **J. Mizrachi:** None. **A. Narasimhan:** None. **X. Qi:** None. **K. Umadevi Venkataraju:** None. **D. Albeanu:** None. **P. Osten:** None.

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Presentation Number: 547.07

Topic: I.04. Physiological Methods

Support: ERC starting grant J17E298
ATIP-Avenir program from CNRS and INSERM
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Simons Foundation Autism Research Initiative Pilot Award (402454)

Title: Whole-brain calcium imaging during physiological vestibular stimulation in larval zebrafish

Authors: G. MIGAULT[1], T. VAN DER PLAS[2], H. TRENTESAUX[1], T. PANIER[1], R. CANDELIER[4], R. PROVILLE[5], B. ENGLITZ[3], G. DEBREGEAS[4], ***V. BORMUTH**[1]; [1]Lab. Jean Perrin, Sorbonne Univ., Paris, France; [3]Neurophysiol., [2]Radboud Univ., Nijmegen, Netherlands; [4]Lab. Jean Perrin, Sorbonne Université/CNRS, Paris, France; [5]Neurocentre Magendie, Physiopathologie de la Plasticite Neuronale, INSERM, U1215, Bordeaux, France

Abstract: The vestibular apparatus provides animals with postural and movement-related information that is essential to adequately execute numerous sensorimotor tasks. In order to activate this sensory system in a physiological manner, one needs to macroscopically rotate or translate the animal's head, which in turn renders simultaneous neural recordings highly challenging. Here we report on a novel miniaturized, light-sheet microscope that can be dynamically co-rotated with a head-restrained zebrafish larva, enabling controlled vestibular stimulation. The mechanical rigidity of the microscope allows one to perform whole-brain functional imaging with state- of-the-art resolution and signal-to-noise ratio while imposing up to 25 in angular position and 6,000/s^2 in rotational acceleration. We illustrate the potential of this novel setup by producing the first whole-brain response maps to sinusoidal and stepwise vestibular stimulation. The responsive population spans multiple brain areas and displays bilateral symmetry, and its organization is highly stereotypic across individuals. Using Fourier and regression analysis, we identified three major functional clusters that exhibit well-defined phasic and tonic response patterns to vestibular stimulation. Our rotatable light-sheet microscope provides a unique tool for systematically studying vestibular processing in the vertebrate brain

and extends the potential of virtual-reality systems to explore complex multisensory and motor integration during simulated 3D navigation.

Disclosures: **G. Migault:** None. **T. van der Plas:** None. **H. Trentesaux:** None. **T. Panier:** None. **R. Candelier:** None. **R. Proville:** None. **B. Englitz:** None. **G. Debregeas:** None. **V. Bormuth:** None.

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Topic: I.03. Anatomical Methods

Support: NIMH 5R01MH100635

Title: Primate brain circuit topographic map revealed by ultra high DSI: 2D retinal GC hexagonal pattern (Polyak, 1953) translates faithfully from optic nerve to 3D thalamic arrays and captures right visual field in left visual cortex

Authors: ***J. R. KORENBERG**[1], F.-C. YEH[5], L. DAI[6], A. N. VAN HOEK[2], E. HSU[3], O. ABDULLAH[7], S. JOSHI[4];
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Abstract: The complex circuitry of the primate visual system is an elegant testament to the central role of light processing in survival throughout the past 550 my of evolution. Organized as the integration of the evolutionarily older “primary” visual system, that then maps on to the visual cortex, a striking feature is the general “retinotopic” organization that is found in most target regions of both systems. How this organization arises from the planar organization (Polyak 1953) seen as a plane of hexagons for retinal ganglion cells (RGC), and how it is translated to the multitude of visual system hubs, is known for only a few basic rules. The fundamental need has been for a technology capable of tracing multiple neighboring axonal bundles from the retina or optic nerve through the complex crossings of the optic chiasm, to target regions. Diffusion spectrum imaging (DSI) provides a theoretical framework to do this but has needed internal systems of known biological structures to be able to evaluate its validity. We report the creation of a heretofore unprecedented dataset of the macaque fascicularis brain that utilized >500 directions, multiple b values of up to 40,000, and 140 h of acquisition in a Bruker 7T with a 20 cm coil. Using the DSI Studio algorithm (Yeh), we generated a series of tests that required successful navigation of multiple DSI challenges including closely spaced crossing fibers in the primate visual system. Further to dimensionally decrease the complex patterns, and to facilitate

pattern detection across 30cm, we developed novel approaches using subvoxel seeding equivalent to micro-voxels of 16-32 micron cubed regions. To align these with high resolution neuroanatomic architecture, we used diffeomorphic transformations to integrate the tracks with a 3D atlas generated from the same animal using block face acquisitions of the complete brain (2300 slices) sectioned at 30microns. We report here two major findings. Axon patterns, presumably represented by the diffusivity of multiple clustered axons, correctly tracked from the right versus the left optic nerve, to reveal a closely apposed pattern of more than 1,000 red versus green signals in the left visual cortex. Second, the findings revealed a pattern of hexagonaly arranged planes that could be followed from each of the optic nerves, through the chiasm and to the lateral geniculate nucleus where the patterns were maintained. These results strongly suggest that DSI combined with histological data, may be suitable for tracing the micro and mesocircuitry of the primate brain.

Disclosures: **J.R. Korenberg:** None. **F. Yeh:** None. **L. Dai:** None. **A.N. Van Hoek:** None. **E. Hsu:** None. **O. Abdullah:** None. **S. Joshi:** None.

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Presentation Number: 547.09

Topic: I.03. Anatomical Methods

Support: UO1NS104370

Title: Genetically targeted fMRI

Authors: *B. B. BARTELLE[1], S. GHOSH[1], N. LI[2], T. XIE[1], A. JASANOFF[3];
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Abstract: Functional magnetic resonance imaging (fMRI) is the dominant technique for measuring brain-wide activity in humans and model mammals, but the method relies on endogenous hemodynamic mechanisms that cannot distinguish the contributions of discrete cell populations and circuit components that comprise neural activity. Here we address this problem by manipulating hemodynamic contrast using a new class of genetically-encodable reporters called NOSTICs. NOSTICs are engineered enzymes that translate intracellular calcium dynamics into production of the potent vasodilator nitric oxide. Implanted NOSTIC-expressing cells induce robust ectopic hemodynamic fMRI signals in live rat brains when stimulated, validating the approach. Importantly, these signals can be selectively inhibited, allowing NOSTIC-dependent activity reports to be dissociated from other hemodynamic signal sources. In conjunction with suitable viral vectors, NOSTIC reporters can be deployed in endogenous brain cells. We show that NOSTIC expression mediated by a retrogradely transported herpes virus permits genetically-

targeted fMRI of neurons presynaptic to viral injection sites in rat striatum. These experiments reveal a constellation of striatal input regions engaged during rewarding stimulation. Our results thus demonstrate an unprecedented tool for selective measurement of cellular activity in deep brain tissue, including spatially-comprehensive analysis of neural circuit function in opaque, living subjects.

Disclosures: **B.B. Bartelle:** None. **S. Ghosh:** None. **N. Li:** None. **T. Xie:** None. **A. Jasanoff:** None.

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Presentation Number: 547.10

Topic: I.04. Physiological Methods

Support: NIH Grant R44MH112273
NIH Grant R44MH112474

Title: High throughput assays of neuronal excitability and synaptic function using all-optical electrophysiology

Authors: *C. A. WERLEY, J. FERRANTE, J. J. FINK, H. SHROFF, G. B. BORJA, G. T. DEMPSEY;
Q-State Biosci., Cambridge, MA

Abstract: Neurological disorders remain a major unmet medical need worldwide, impacting nearly 1 billion people globally. The discovery of new drugs for diseases of the nervous system continues to be a major challenge for the pharmaceutical industry - development timelines are longer and the approval rate is lower than for drugs targeting other therapeutic areas. New approaches are needed. Here we present high-throughput, all-optical electrophysiolgy methods for assaying neuronal excitability and synaptic signaling using a robust, industrial-scale platform that can be applied in drug screening.
“Optopatch” allows simultaneous optical stimulation and recording of neuronal action potentials (APs) and sub-threshold voltage changes using genetically encoded proteins: the engineered channelrhodopsin CheRiff enables AP stimulation with blue light and the engineered voltage-sensitive fluorescent protein QuasAr enables high-speed electrical recordings with red light. Optopatch maintains the rich information content of manual patch clamp by faithfully recording changes in membrane potential, but with a huge reduction in labor. The platform is compatible with a variety of primary and human induced pluripotent stem cell-derived neurons (hiPSC-neurons).
These optogenetic tools are paired with the Firefly microscope, which routinely makes

simultaneous voltage recordings from >100 individual neurons over a large (0.5 x 4 mm) field of view with 1 ms temporal resolution and high signal-to-noise (SNR). The fully automated system is compatible with 96-well plates and can record from ~800 wells/day, which enables screening, e.g. for compounds that reverse a disease phenotype in patient-derived iPSC-neurons. Neuronal excitability is assayed by measuring neuronal spike rate and AP shape in response to a variety of optogenetic stimuli. Dimensionality reduction is used to capture the multifactorial disease phenotype in a single number that serves as the basis for screening. The assay has identified several phenotypes from monogenic disorders and can distinguish effects from compounds modulating diverse ion channel targets. Synaptic function is assayed by recording excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs) in individual postsynaptic cells in response to optogenetic stimulation of a distinct set of presynaptic neurons. The assay is sensitive to presynaptic and AMPA, NMDA, and GABAA receptor modulators. Early results indicate robust measures of synaptic plasticity. Together, these assays enable phenotyping and drug screening at a throughput that was previously impossible using incisive electrophysiology measurements.

Disclosures: **C.A. Werley:** A. Employment/Salary (full or part-time):; Q-State Biosciences. **J. Ferrante:** A. Employment/Salary (full or part-time):; Q-State Biosciences. **J.J. Fink:** A. Employment/Salary (full or part-time):; Q-State Biosciences. **H. Shroff:** A. Employment/Salary (full or part-time):; Q-State Biosciences. **G.B. Borja:** A. Employment/Salary (full or part-time):; Q-State Biosciences. **G.T. Dempsey:** A. Employment/Salary (full or part-time):; Q-State Biosciences.

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

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Topic: I.03. Anatomical Methods

Support: German Research Foundation KU 2474/13-1
German Research Foundation SCHW 1578/2-1
German Research Foundation SFB 1089/P03

Title: Light sheet fluorescence expansion microscopy and serial block face sectioning: Complete mapping of extended neuronal circuits at super resolution

Authors: *J. E. RODRIGUEZ GATICA[1], I. PAVLOVA[2], J. SCHWEIHOFF[2], J. P. SIEBRASSE[1], M. K. SCHWARZ[2], U. KUBITSCHECK[1];
[1]Inst. of Physical and Theoretical Chem., [2]Inst. of Exptl. Epileptology and Cognition Res., Rheinische Friedrich-Wilhelms-University Bonn, Bonn, Germany

Abstract: The combination of tissue expansion and light sheet fluorescence microscopy allows extended volumetric super resolution imaging of large mouse brain samples at high speed (1, 2). Recently, we demonstrated the capabilities of this method by performing three color imaging of mouse CA1 and dentate gyrus molecular-, granule cell- and polymorphic layers. This approach features (i) high imaging rates, (ii) high contrast, (iii) low photobleaching, (iv) lateral sample extensions in the centimeter range and (v) effective optical super resolution. Even more, a careful sample preparation allows preserving the fluorescence of autofluorescent proteins. However, when imaging thicker samples we encountered the problem that the final (expanded) sample size exceeds the working distance of high resolution objective lenses. Sectioning the sample before imaging results in artifacts and distortions that prohibit reconstructing intact neuronal circuits. Here we solve this problem by combining Light Sheet Fluorescence Expansion Microscopy and serial block face sectioning of the expanded samples in the same instrument using a custom-developed microtome. This should allow to image samples with virtually unlimited axial extensions.
(1) Bürgers J., Pavlova I., Rodriguez J.E. *et al.* Light-sheet fluorescence expansion microscopy: fast mapping of neural circuits at super resolution. *Neurophoton* **6,** 015005 (2019).
(2) Gao, R. *et al.* Cortical column and whole-brain imaging with molecular contrast and nanoscale resolution. *Science* **363,** eaau8302 (2019).

Disclosures: J.E. Rodriguez Gatica: None. **I. Pavlova:** None. **J. Schweihoff:** None. **J.P. Siebrasse:** None. **M.K. Schwarz:** None. **U. Kubitscheck:** None.

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

Location: Room S106

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 547.12

Topic: I.04. Physiological Methods

Support: NIH Director’s New Innovator IDP20D017782-01
Presidential Early Career Awards for Scientists and Engineers (PECASE)
NIH BRAIN RF1MH117069
NSF NeuroNex Technology Hub1707316
Tianqiao and Chrissy Chen Institute for Neuroscience
Heritage Medical Research Institute
Children's Tumor Foundation Young Investigator Award 2016-01-006

Title: Optical monitoring of dopamine dynamics with dLight1.2 in a mouse model of neurofibromatosis type 1

Authors: *J. E. ROBINSON[1], G. M. COUGHLIN[1], A. M. HORI[1], J. R. CHO[1], T. PATRIARCHI[2], L. TIAN[2], V. GRADINARU[1];

[1]Biol. and Biol. Engin., Caltech, Pasadena, CA; [2]Biochem. and Mol. Med., Univ. of California, Davis, Davis, CA

Abstract: Recent advances in the development of genetically encoded neurotransmitter sensors has improved the ability to detect neurotransmission with high sensitivity and temporal resolution in freely moving rodents over months of testing. In these studies, we used the optical dopamine sensor dLight1.2 to monitor fluorescent dopamine dynamics in the lateral nucleus accumbens during motivated behavior in a mouse model of neurofibromatosis type 1 (NF1), an autosomal dominant disorder caused by mutations in the *NF1* gene that is associated with deficits in executive function, attention, and spatial learning. Previous studies suggest that these phenotypes are due to developmental perturbations in mesolimbic dopamine circuitry, however, these circuits have never been directly assayed *in vivo* in NF1 model mice. Using dLight1.2 (PMID: 29853555), we found that *Nf1*$^{+/-}$ mice exhibit differences in basal dopaminergic neurotransmission and responses to salient visual stimuli, which we further parsed *ex vivo* using patch clamp electrophysiology, tissue clearing, and new systemic AAV vectors (*Th*-VAST) optimized to provide sparse, multicolor, recombinase-independent labeling of catecholaminergic neurons and facilitate reconstruction of dendritic arbors. These studies provide the first ever *in vivo* characterization of dopaminergic circuit function in the context of NF1, reveal novel pathophysiological mechanisms influencing cognitive sequelae of the disease, and introduce new viral tools for morphological characterization of dopaminergic populations.

Disclosures: J.E. Robinson: None. **G.M. Coughlin:** None. **A.M. Hori:** None. **J.R. Cho:** None. **T. Patriarchi:** None. **L. Tian:** None. **V. Gradinaru:** None.

Nanosymposium

547. New Technologies for Imaging Neuronal Structure and Activity

Location: Room S106

Time: Tuesday, October 22, 2019, 1:00 PM - 4:15 PM

Presentation Number: 547.13

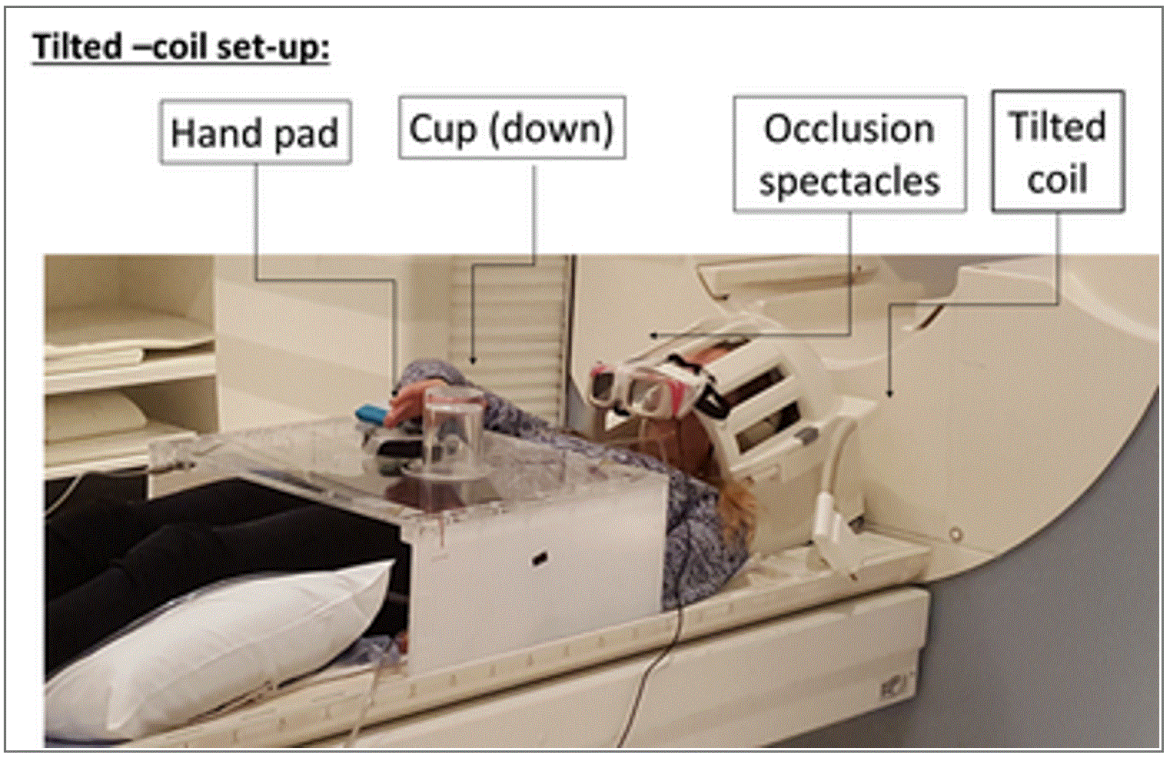
Topic: E.04. Voluntary Movements

Support: Academy of Medical Sciences grant to ER

Title: The role of familiarity in object manipulation: An ’object in the fMRI scanner’ study

Authors: *E. ROUNIS[1], Z. ZHANG[2], N. NELISSEN[3], N. FILIPPINI[3], P. ZEIDMAN[4], J. DIEDRICHSEN[5];
[1]Oxford Univ., Oxford, United Kingdom; [2]MRC Social, Genet. and Developmental Psychiatry Ctr., King’s Col. London, London, United Kingdom; [3]Univ. of Oxford, Oxford, United Kingdom; [4]UCL Inst. of Neurology, London, United Kingdom, London, United Kingdom; [5]Brain and Mind Inst., Western Univ., London, ON, Canada

Abstract: Behavioural studies have shown that perception of object features can potentiate motor components of possible actions. We have previously shown that healthy participants were faster when initiating movements to manipulate a cup, when the orientation of its opening (cup upright or inverted) matched the orientation of the hand (straight or inverted)1. Previous studies have suggested a network of brain regions involving the dorsal premotor cortex when selecting motor responses relating to object grasp orientations2. Here we tested the effect of cup orientation on actions performed during BOLD fMRI, to study the neural underpinnings of familiarity effects, identified in our behavioural study. 25 right-handed participants were scanned in a 'Object in the scanner' environment. They were asked to turn a handless glass, which was presented to them on a table on which they rested their hand, either in the upright or inverted positions. We quantified brain BOLD activity in an event related fMRI design, following an instruction specifying the goal-directed action to make: turning the glass with a 'straight' or an 'inverted' hand posture (Figure 1, experimental set-up). We found that cup orientation modulated movement initiation times measured by the lifting of participants' hand from a resting pad on the table. Participants were faster when grasping the glass from its opening, independent of the goal-directed action they were asked to do. The task activated a wide network of brain regions known to be involved in hand-object interactions2: planning action initiation activated bilateral prestriate areas, superior temporal gyri, the left superior parietal gyrus, and left premotor and motor areas. We found modulation of the bilateral dorsal premotor cortices (PMd), when planning a grasp directed to opening end of the glass. This study confirms a role for dorsal premotor cortex in selecting amongst competing hand postures2. References: 1. Rounis E, et al. (2017) Experimental Brain Research 235:1281-1296. 2. Grèzes J, et al. (2003) European Journal of Neuroscience 17:2735-2740.



Disclosures: **E. Rounis:** None. **Z. Zhang:** None. **N. Nelissen:** None. **N. Filippini:** None. **P. Zeidman:** None. **J. Diedrichsen:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.01

Topic: A.04. Transplantation and Regeneration

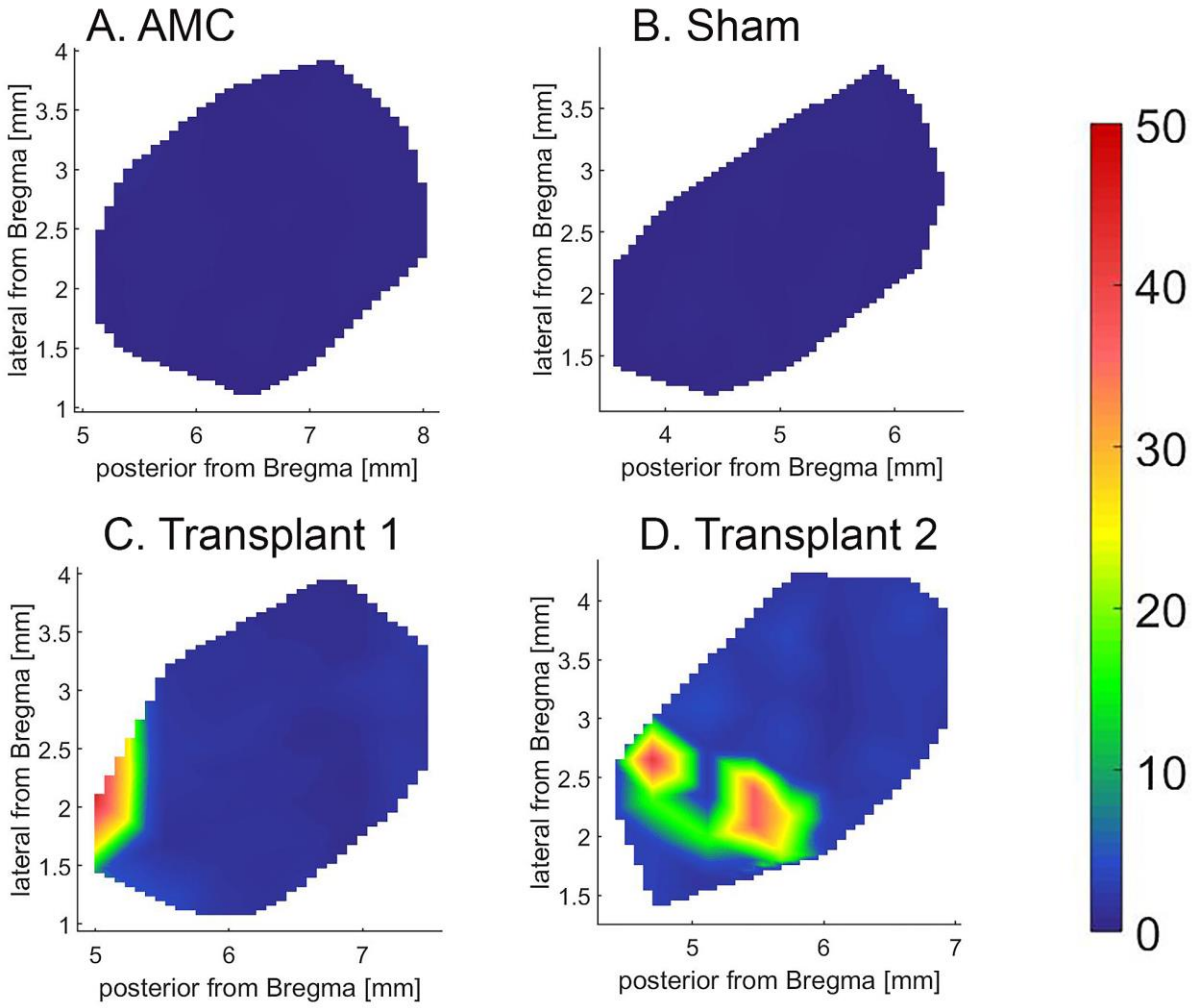
Support: 1R44EY027654-01A1

Title: Transplantation of human embryonic stem cell derived retinal sheets improves vision in immunodeficient rats with retinal degeneration

Authors: *I. O. NASONKIN[1], R. SINGH[1], F. BINETTE[1], B. LIN[2], P. A. WINKLER[3], R. B. ARAMANT[2], M. J. SEILER[4];
[1]Biotime, Inc., Alameda, CA; [2]Stem Cell Res. Center, Univ. of California- Irvine, Irvine, CA; [3]Small Animal Clin. Sci., Michigan State Univ., East Lansing, MI; [4]Dept. of Physical Med. & Rehabilitation, Dept. of Ophthalmology (joint appointment), Sue and Bill Gross Stem Cell Res. Center, Univ. of California, Irvine, Irvine, CA

Abstract: We present the structural and functional integration of hESC-derived retinal sheets in the subretinal space of immunodeficient RD rats *SD-Foxn1 Tg(S334ter)3Lav* (*RD nude*), and Royal College of Surgeons (*RCS nude*) as a 1st step for developing a bioprosthetic retinal implant for restoring functional vision. We derived retinal organoids from WA01(H1) hESC line (Singh et al., Stem Cells & Devel., 2015), with modifications, and demonstrated the presence and distribution of eyefield (RX, PAX6), retinal progenitor (CHX10, NEUROD1), photoreceptor [PR] (BLIMP1, CRX, RCVRN, OTX2), 2nd order neuron (CALB2) and ganglion cell (BRN3) markers, typical of human fetal retinal tissue age 10-15 weeks (RNA-seq and immunohistochemistry). We also found that more mature (~5-6 month old) hESC-retinal tissue has numerous inner-outer segment protrusions and cilia (electron microscopy data) and a dense layer of rod (RHO, RDS, RCVRN) and cone (OPN1SW, RXRɣ, RCVRN) PRs. We transplanted retinal tissue from rims of organoids into the subretinal space of *RD nude* and *RCS nude* rats and followed the grafts with spectral domain optical coherence tomography (OCT). We noted initial improvement of light responses with the optokinetic test (evaluating spatial frequency threshold), and robust activation of contralateral superior colliculus (SC) at least 5 months after transplantation. Age-matched RD rats without graft and sham-surgery RD rats had no activity in SC in response to light. In transplanted rats, immunostaining demonstrated robust donor and host synaptic connectivity (human-specific SYP antibody), and abundant presence of human rod and cone PRs. Critically, some PRs displayed long outer segments with typical outer segment markers. These data, collectively, delineate the feasibility of restoring light perception with

retinal tissue implanted into the subretinal space and pave the way for developing the larger bioprosthetic retinal implants for restoring functional vision.



Disclosures: **I.O. Nasonkin:** None. **R. Singh:** None. **F. Binette:** None. **B. Lin:** None. **P.A. Winkler:** None. **R.B. Aramant:** None. **M.J. Seiler:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.02

Topic: A.04. Transplantation and Regeneration

Support: T32 EB006359

Title: Calcium imaging for stem cell grafts in mouse neocortex: Continuous tracking and assessment of functional integration

Authors: *S. S. CHA, M. E. BUCKLIN, X. HAN;
Boston Univ., Boston, MA

Abstract: The therapeutic potential of stem cells, due to their ability to differentiate into multiple specialized cell types and capacity for limitless expansion, makes them a promising vehicle for repairing and replacing damaged cells in neurodegenerative diseases. Preliminary clinical trials of stem cell therapies in stroke and Parkinson's disease report that transplantation can lead to symptomatic relief in patients. Nevertheless, stem cell therapies for neurodegenerative disorders are still at an early stage of development, and a better understanding of how to induce functional integration of stem cell-derived neurons is essential for clinical translation. However, only a limited number of tools are available to observe grafted stem cells and to monitortheir development process. We have recently developed a polymer-based optical imaging implant that allows tissue access for stem cell transplantation and maintains optical clarity throughout the study period. Utilizing the system, we have grafted neural progenitor cells into an adult mouse cortex, and imaged the neuronal activity of the progenitor cell-derived neurons at the same region over several months, using a wide-field epifluorescence microscope. The development of this imaging technique is important for a more thorough assessment of stem cell engraftment in the brain and will ultimately help advance stem cell therapy for neurodegenerative disorders.

Disclosures: S.S. Cha: None. **M.E. Bucklin:** None. **X. Han:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.03

Topic: A.04. Transplantation and Regeneration

Support: NYSTEM

Title: Neovascularization for optimal survival of neural transplants

Authors: *J. E. KRZYSPIAK[1], J. YAN[1], B. GALINSKI[1], P. J. LITUMA[1], S. WASHBURN[1], P. E. CASTILLO[2], D. WEISER[1], S. ZUKIN[1], K. KHODAKHAH[3], J. M. HEBERT[1];
[1]Albert Einstein Col. of Med., Bronx, NY; [2]Albert Einstein Coll Med., Bronx, NY; [3]Dept Neurosci., Albert Einstein Col. Med., Bronx, NY

Abstract: The transplantation of neural stem cells holds great promise for improving function in the aging brain. Days or weeks after transplantation, however, transplant-derived cells can be

greatly reduced in numbers. The loss of transplanted cells has been attributed in part to immunorejection. However, there is growing evidence in the field that supporting cell types may be required to facilitate the success of a transplant in contrast to transplanting pure populations of cells. Specifically, there is evidence that neovascularization may be critical for transplant cell survival. As in the fetus where vascularization must match the physiological demands of each growing tissue, vascularization of neural cell transplants might also need to occur rapidly to promote optimal neuron survival, differentiation, and function. Our preliminary studies with transplants of embryonic forebrain cells into the young adult neocortex of unaffected and stroke-affected mice suggest that vascular endothelial precursors may be required in the transplant cell population for efficient survival of the neural precursors and the neurons they generate. We observe that within transplants on the stroke affected side, blood vessels primarily develop from donor-derived cells, in contrast to the control side, and appear to fuse with the host vasculature. The process of neovascularization in the aging brain differs from young subjects in several aspects including reductions in hypoxia-induced angiogenesis, the release of angiogenic growth factors, and expression of receptors, all of which underscore the importance of including vascular precursors in a neural transplant. We are currently determining the importance of including vascular cells with neural cells when transplanting to old (24 month) mice. To show that donor-derived vessels are integrating with the host circulation, we are using an intravenous fluorescent dye to confirm bona fide fusion with host vessels. To determine the requirement of vascular precursor cells for enhanced cell survival, we are currently experimenting with two mixes of cell types for transplantation: one that contains the complete heterogeneous population of cells harvested from mouse embryonic cortices and one that lacks specifically the vascular precursor cells. We are also testing the ability of human embryonic stem cell derived neural stem cells and human umbilical cord and brain derived endothelial cells for their ability to survive and integrate into the neocortex. These studies are directly relevant to the effective use of neural cell transplants in future clinical trials.

Disclosures: **J.E. Krzyspiak:** None. **J. Yan:** None. **B. Galinski:** None. **P.J. Lituma:** None. **S. Washburn:** None. **P.E. Castillo:** None. **D. Weiser:** None. **S. Zukin:** None. **K. Khodakhah:** None. **J.M. Hebert:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.04

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant R01 NS110936-01

Title: Poly ADP-ribosylation regulates multiple independent molecular mechanisms to determine whether the injured nervous system achieves functional axon regeneration

Authors: M. BELEW, ***A. B. BYRNE**;
UMass Med. Sch., Worcester, MA

Abstract: To fully repair injured neurons, our nervous systems must regenerate damaged axons and rebuild synapses with interacting cells, a process called functional axon regeneration. However, injury often results in permanent deficits because many adult neurons, including those in the central nervous system, are not capable of functional axon regeneration after injury. Unfortunately, the intrinsic molecular mechanisms that regulate functional axon regeneration are not well understood. Identifying and characterizing these molecular mechanisms will not only enhance our understanding of how to repair the injured adult nervous system, it will also add to our understanding of the mechanisms that regulate post-developmental axon growth and synapse formation. We recently found poly (ADP-ribosylation) functions intrinsically to regulate functional axon regeneration of individual severed GABA motor neurons *in vivo*. In addition, we have now identified two independent molecular mechanisms by which poly (ADP-ribose) polymerases inhibit functional axon regeneration. Defining how poly (ADP-ribosylation) regulates functional axon regeneration both adds to our understanding of the intrinsic mechanisms that regulate neuronal repair and contributes to strategies to improve functional axon regeneration after injury.

Disclosures: M. Belew: None. **A.B. Byrne:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.05

Topic: A.04. Transplantation and Regeneration

Support: 5U01EY027267-03

Title: Comparative analysis of single-cell transcriptomes and epigenomics in retinal injuries and glia-mediated regeneration in the vertebrate retina

Authors: *T. V. HOANG[1], J. WANG[1], P. BOYD[2], C. SANTIAGO[1], A. FISCHER[3], J. D. ASH[4], D. R. HYDE[2], J. QIAN[1], S. BLACKSHAW[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Univ. of Notre Dame, Notre Dame, IN; [3]Ohio State Univ., Columbus, OH; [4]Ophthalmology, Univ. of Florida, Gainesville, FL

Abstract: One potentially important approach to restore vision is the regeneration of lost retinal neurons from an endogenous population of retinal cells, the Müller glia. However, retinal Müller

glia show dramatic differences in neurogenic competence among different species. Zebrafish have an extraordinary capacity to completely regenerate photoreceptors following injury, via controlled dedifferentiation of retinal glia. Chick glia show a limited regenerative ability while mice, like humans, have completely lost the ability to regenerate retinal neurons. To explore the potential of ultimately stimulating the resident Müller glia in the damaged human retina, we have conducted a comprehensive and unbiased, comparative analysis of gene expression and chromatin conformation of Müller glia in zebrafish, chick, and mouse retinas during retinal development and in multiple injury models using single-cell RNA-Seq, total RNA-Seq and ATAC-Seq. We performed sequencing of over 100 total RNA-Seq and 40 ATAC-Seq of FACS-purified Müller glia samples at multiple time points under two different retinal injury models (NMDA damage and light damage) in all three species. In addition, we performed single-cell RNA-Seq on over 300,000 cells at multiple time points during normal retinal development and in damage models in all three species. Our analysis found that zebrafish Müller glia undergo a very transient gliotic state and quickly move to neurogenesis after retinal damages, while these processes are relatively slower in chick Müller glia. In constrast, mouse Müller glia are locked in gliotic state after injuries. We have found that in zebrafish, to some extents, Müller glia-mediated retinal regeneration is a reversed process of retinal development. We have also constructed transcriptional networks and identified a large number of genes that are switched on or off following injury in all three species. Some of these are strongly up- or down-regulated in fish, weakly up or down-regulated in chick, and not expressed in mice. Others show opposite patterns of regulation, being strongly up- or down-regulated in mice, slightly in chick, and not in zebrafish. These represent genes that are excellent candidates for respectively promoting or inhibiting the ability of retinal glia to give rise to neurons following injury. We tested the roles of the several candidate genes in Müller glia reprogramming in the damaged zebrafish and chick retina. By up or down-regulated different combinations of these candidate genes in mouse, we are working to develop approaches that will enable mouse retinal glia to regenerate neurons.

Disclosures: **T.V. Hoang:** None. **J. Wang:** None. **P. Boyd:** None. **C. Santiago:** None. **A. Fischer:** None. **J.D. Ash:** None. **D.R. Hyde:** None. **J. Qian:** None. **S. Blackshaw:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: Department of Veterans Affairs Grant I21RX002876
Department of Veterans Affairs Grant I21RX002069
Department of Veterans Affairs Grant 1I21RX003019
Department of Veterans Affairs Grant 1I01BX0004067

Department of Veterans Affairs Grant I01RX002660
Department of Veterans Affairs Grant 1I01RX000996
National Institutes of Aging Grant P50AG11508

Title: Hemovasculogenic origin of the brain vasculature in the developing mouse

Authors: *M. A. GAMA SOSA[1], R. DE GASPERI[2], G. M. PEREZ[2], P. R. HOF[4], G. A. ELDER[3];
[1]Gen. Med. Res. Service, [2]Res. & Develop., [3]Neurol. Service, James J. Peters VA Med. Ctr., Bronx, NY; [4]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Vascular formation in the developing brain is thought to form by angiogenesis from preformed blood vessels in the cephalic mesenchyme. Immunohistochemical studies of vascular development in the mouse brain (E10.5 to E13.5) revealed the presence of avascular blood islands of primitive erythroid cells expressing hemangioblast markers (Flk1, Tal1/Scl1, PECAM1, VE-cadherin and CD34) and an endothelial marker recognized by *Griffonia simplicifolia* isolectin B4 in the cephalic mesenchyme. These cells formed a perineural vascular plexus from which angiogenic sprouts originated and penetrated the neuroepithelium. In addition, avascular isolated cells expressing primitive erythroid, hemangioblast and endothelial makers were visible in the neuroepithelium where they generated vasculogenic and hemogenic foci. At E10.5 to E13.5 these vasculogenic foci were the major source of new blood vessel formation in the developing brain. *In vitro*, cultures of E13.5 brain endothelial cells contained hemogenic endothelial cells capable of generating erythroid cells. Similar cells were present in primary cultures of dissociated cells from E10.5 embryonic head. Our results provide new evidence that the brain vasculature, like that of the choriocapillaris and hyaloid vascular systems in the eye, develops in large part by a process of hemovasculogenesis, in which vasculogenesis and hematopoiesis occur simultaneously.

Disclosures: M.A. Gama Sosa: None. **R. De Gasperi:** None. **G.M. Perez:** None. **P.R. Hof:** None. **G.A. Elder:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.07

Topic: A.01. Neurogenesis and Gliogenesis

Title: Recapitulation of the areal patterning in the cerebral cortex by human ESC/iPSC-derived cortical neurons

Authors: *K. IMAIZUMI, H. OKANO;
Dept. of Physiology, Keio Univ., Tokyo, Japan

Abstract: The cerebral cortex is subdivided into distinct areas that have particular functions. The rostrocaudal (R-C) gradient of fibroblast growth factor 8 (FGF8) signaling defines this areal identity during neural development. However, the mechanism of areal patterning has mostly been studied in mouse models, and it is unclear whether the findings can be applied to human cerebral cortex development. In this study, we recapitulated cortical R-C patterning in human embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC) cultures. Modulation of FGF8 signaling appropriately regulated the expression of R-C markers, and the correlation analysis with human *in vivo* fetal brain transcriptome showed that FGF8 treatment conferred rostral (the sensorimotor cortex) identity on ESC/iPSC-derived cells, whereas these cells retained caudal (the temporal lobe) identity in the absence of FGF8. Our data suggest that the areal patterning can be precisely controlled in human ESC/iPSC cultures. Moreover, the area-specific forebrain phenotypes of *ALS2*-associated amyotrophic lateral sclerosis (ALS) were reproduced in vitro by using this system. We here present the first evidence of modeling the upper motor neuron phenotypes of ALS *in vitro* and our results represent an important step in the study of ALS. Finally, we will show preliminary results of the recapitulation of the FGF8-driven R-C axis formation in ESC/iPSC-derived cerebral organoids, and will discuss the mechanism underlying the precise establishment of the R-C axis within these organoids.

Disclosures: K. Imaizumi: None. **H. Okano:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.08

Topic: A.01. Neurogenesis and Gliogenesis

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

Title: Investigation of the mechanisms underlying gyrification of the cerebral cortex using gyrencephalic ferrets

Authors: *H. KAWASAKI, Y. SHINMYO, N. MATSUMOTO;
Sch. of Med, Kanazawa Univ., Kanazawa, Japan

Abstract: Folds of the cerebral cortex, which are called the gyri and the sulci, are one of the most prominent features of the mammalian brain. To investigate the mechanisms underlying the formation of cortical folds, we developed a genetic manipulation technique for the cerebral cortex of gyrencephalic carnivore ferrets using in utero electroporation. Genes-of-interest can be expressed in the ferret cortex rapidly and efficiently. We also demonstrated that genes-of-interest can be knocked out in the ferret cortex by combining in utero electroporation and the CRISPR/Cas9 system. Using our technique, we uncovered that FGF signaling is necessary and sufficient for cortical folding. We found that overexpression of FGF8 induced additional gyri, and that suppression of FGF signaling inhibited cortical folding. In addition, we found that the thickness of upper layers was preferentially affected by FGF signaling, raising the possibility that upper layers are important for cortical folding. Consistently, when radial migration of upper-layer neurons was suppressed by inhibiting Cdk5, cortical folding was inhibited. Our findings provide in vivo data about the mechanisms of cortical folding in gyrencephalic mammals. Our technique for the ferret cerebral cortex should be useful for investigating the mechanisms underlying development and diseases related to brain structures unique to higher mammals, which cannot be investigated using mice.

Disclosures: H. Kawasaki: None. **Y. Shinmyo:** None. **N. Matsumoto:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.09

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant DA02399
NIH Grant EY002593
NIH Grant MH113257
MacBrain Resource

Title: The foundations of cerebral gyrification in primates

Authors: *B. G. RASH, P. RAKIC;
Neurosci., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Towards the end of the 20th century, it was generally recognized that cerebral gyrification is induced by a variety of genetically specified mechanical factors—chiefly the expansion of the cortical surface and asymmetric growth of subjacent white matter tracts.

However, recent studies have instead proposed a role for localized neurogenesis ‘hot spots’ in the proliferative outer subventricular zone (oSVZ), arranged in a proto-gyral pattern. However, new and previous DNA replication data in the developing macaque indicate that neurogenesis and, as we show here, settling of neurons into the cortical plate, are finished prior to gyral development. In fact, the principal contribution of the oSVZ during the period of gyrification is the production of oligodendrocytes and astrocytes, not neurons (Rash et al., 2019). In addition, we demonstrate that explosive neuropil growth following the cessation of neurogenesis results in a ~15-fold decrease in neuronal density in the cortex, occurring during the period of most rapid gyral development from the 100th embryonic day to birth, expanding cortical surface area and inducing convolutions. Sulcal deepening and gyral development continue beyond at least the 3rd postnatal month. Strikingly, we also find that the experimental elimination of thalamocortical axonal inputs to the visual cortex, due to ocular enucleation, exerts a profound impact on gyral pattern that is also independent of the preceding neurogenesis. Thus, we conclude that localized neurogenesis in the oSVZ cannot account for gyral development in primates. Instead, we find that gyrification requires a sufficient number of radial units, generated by founder stem cells in the ventricular zone, as well as subsequent, explosive growth in the size of neuronal cell bodies and neuropil, augmented by addition of glial cells, and the massive, spatio-temporally asymmetric growth of subjacent white matter tracts.

Disclosures: B.G. Rash: None. **P. Rakic:** None.

Nanosymposium

626. Neural Differentiation, Transplantation, and Regeneration

Location: Room S505

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 626.10

Topic: A.01. Neurogenesis and Gliogenesis

Support: Thailand Research fund (IRN58W0004)

Title: A novel methodology to induce differentiation of a neuronal cell line, cath.a-differentiated cell

Authors: *E. KHONGKLA, W. SAENGSAWANG;
Physiol., Mahidol Univ., Bangkok, Thailand

Abstract: CAD (Cath.a-differentiated) cells is a cell line established from mouse CNS catecholaminergic neuron. They can be maintained in the proliferative phase in the presence of serum and can be induced to differentiate into neuron-like cells simply by removing serum from culture medium. Differentiated CAD cells extend long neurites and express several neuron-specific proteins resembling primary neurons, making it a suitable neuronal cell model for studying several aspects of neurons. However, with the current differentiation method, the

differentiated CAD cells cannot be maintained for a long period of time. Thereby, a new method that can effectively differentiate and maintain survival of the differentiated CAD cells is required. Glucocorticoid (GC), a stress-responded hormone has been shown to play a role in the neuronal development. Even though it has been reported that GC can promote differentiation of neural progenitor cells (NPCs), the effect of GC on CAD cell differentiation is unknown. Here we demonstrate that dexamethasone (DEX), a synthetic GC, not only rapidly induced CAD cell differentiation but also prolonged their survival for at least a month. In the presence of 8% serum CAD cells continued to proliferate and showed polygonal shape without any neurites. Only one day of incubation with 100 uM of DEX the CAD cells stopped proliferation and began to extend long neurite-like processes. Western blot analysis and immunofluorescence imaging revealed that DEX-differentiated CAD cells expressed neuronal specific proteins, particularly βIII-tubulin. In addition, cell viability assays showed that survival of the CAD cells differentiated by DEX was significantly prolonged when compared to the CAD cells differentiated by serum-free condition. These evidences suggested that dexamethasone could be used as a novel method for CAD cell differentiation, which will be a useful tool for several aspects of neuroscience research.

Disclosures: E. Khongkla: None. **W. Saengsawang:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.01

Topic: A.07. Developmental Disorders

Support: Telethon Grant TI-TCP15021

Title: Characterization of the brain Na-K-Cl importer NKCC1 structure-function relationship

Authors: *C. PORTIOLI[1,3], M. DE VIVO[2], M. ZHOU[3], L. CANCEDDA[1,4];
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Abstract: The inhibitory neurotransmitter GABA, through Cl-permeable $GABA_A$ receptors, is fundamental in physiological neurodevelopment. Defective $GABA_A$ergic transmission is present in numerous brain disorders. Pharmacological treatments are urgently needed. Increasing evidence has demonstrated that modulation of $GABA_A$ergic transmission by varying intracellular Cl concentration (mainly established by the Cl importer NKCC1 and the Cl exporter KCC2) is safer than direct blockade of the receptor. Importantly, NKCC1/KCC2 ratio is defective in numerous brain diseases, and NKCC1 inhibition by the FDA-approved drug bumetanide rescues many symptoms in animal models. This has motivated clinical studies for the chronic usage of

bumetanide in a broad range of brain disorders. However, bumetanide is a strong diuretic due to the inhibition of the kidney Cl importer NKCC2, which makes it not suitable for chronic treatments in terms of drug compliance. Crucially, this issue would be solved by selective NKCC1 inhibitors, thus devoid of the diuretic effect. Here, we aim at solving the still unknown NKCC1 structure, by cutting-edge techniques including cryo-electron microscopy (cryo-EM) and/or X-ray crystallography, and at elucidating the structure-function relationships for NKCC1 ion transportation. First, we tested 20 full-length and 9 truncated NKCC1 homologs by small-scale HEK transient transfection coupled with fluorescence-detection, size-exclusion chromatography for monodispersity and expression level evaluation. Thus, we identified the optimal candidates for structure resolution. We then generated BacMam viruses and used them for medium-scale HEK cell transduction. We extracted membrane proteins, separated them from the insoluble fraction, and purified them by size-exclusion chromatography. These results will enable us to achieve large-scale protein expression required for structural (cryo-EM, X-ray crystallography, nanodiscs and amphipols) and functional studies (binding and transport assays). Characterizing NKCC1 structure will be a breakthrough advance in the understanding of NKCC1 ion-transport mechanism and it will critically accelerate the rational design and discovery of new, selective NKCC1 inhibitors urgently needed for the treatment of brain disorders.

Disclosures: C. Portioli: None. **M. De Vivo:** None. **M. Zhou:** None. **L. Cancedda:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.02

Topic: A.07. Developmental Disorders

Support: LeJeune Foundation
NIH R01 NS086933-01
Linda Crnic Foundation

Title: Sleep architecture changes in a mouse model of Down syndrome

Authors: *P. CAIN[1], H. WONG[1], C. BORSKI[1], A. COOPER SANSONE[1], L. LAPLANTE[1], J. LEVENGA[2], C. HOEFFER, Jr.[1,3,4];
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Abstract: Down syndrome (DS) is a neurodevelopmental disorder caused by an extra copy of human chromosome 21 (HSA21). Approximately 60% of the DS population displays sleep disturbances. HSA21 carries approximately 250 genes and sleep is known to be under strong

genetic control. The sleep disturbances are often caused by sleep apnea, but previous research also has shown sleep to be altered independently of apnea. These alterations consist of increased latency to NREM, sleep fragmentation, and reduced REM. While EEG activity is altered in DS brains during steady state and cognitive tasks, EEG abnormalities in DS sleep disruptions are only recently becoming better characterized. In the mouse, chromosome 16 is homologous to HSA21 and in the DS mouse model *Dp(16)1Yey/+ (Dp16*), only chromosome 16 is triplicated. In addition, the *Regulator of Calcineurin1* (*RCAN1*) gene is located on HSA21 and syntenic on mouse chromosome 16, so its triplication results in increased levels of RCAN. Our lab previously demonstrated that sleep and EEG activity were disrupted in aged *Dp16* mice and these disturbances mirrored earlier findings in the DS population (Levenga et al., 2018). We hypothesized that 3-6 mo. male and female Dp16 mice would show disrupted sleep architecture as compared to wild-types (WT). We also hypothesized that RCAN1, known to influence innate anxiety and anxiogenic responses (Hoeffer et al., 2013), might be involved with sleep disruption. Re-establishing more normal RCAN1 levels with *Dp16* mice heterozygous for an *Rcan1* knockout gene (*Dp16 Rcan1*^{2N}) might reduce sleep disruptions. In this study, we characterize and compare for the first time the sleep architecture and EEG activity in 3-6 mo. old male and female WT, *Dp16*, and *Dp16 Rcan1*^{2N} . Our data support the theory that the effects of chromosome 16 triplication are age-related with impact increasing over time. The effects on sleep architecture of re-establishing normal levels with RCAN1 expression on a *Dp16* background are not immediately apparent.

Disclosures: P. Cain: None. **H. Wong:** None. **C. Borski:** None. **A. Cooper Sansone:** None. **L. LaPlante:** None. **J. Levenga:** None. **C. Hoeffer:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.03

Topic: A.07. Developmental Disorders

Title: Restoring neuronal chloride homeostasis by anti NKCC1 gene therapy rescues cognitive deficits in a mouse model of Down syndrome

Authors: *A. CONTESTABILE[1], M. PARRINI[1], S. NASKAR[1], M. ALBERTI[1], M. NANNI[1], G. RONZITTI[2], F. MINGOZZI[2], L. CANCEDDA[1,3];
[1]Fondazione Inst. Italiano Di Tecnologia, Genoa, Italy; [2]Genethon, Evry, France; [3]Telethon Dulbecco Inst., Genoa, Italy

Abstract: The Ts65Dn mouse model of Down syndrome (DS) exhibits cognitive deficits that have been largely attributed to alteration of GABAergic signaling. In particular, increased intracellular chloride concentration mediated by an upregulation of the expression of the chloride

importer NKCC1, which is also increased in the brains of individuals with DS, shifts the polarity of $GABA_A$-mediated responses from hyperpolarizing to depolarizing in Ts65Dn brains. In order to validate NKCC1 as a molecular target for cognitive deficits in DS and open the possibility for a future gene-therapy approach to treat the disease, we have here investigated whether normalization of NKCC1 activity could rescue cognitive deficits in Ts65Dn mice. In particular, we have developed and optimized a RNA-interference approach to knockdown NKCC1 expression. Our results show that reducing the expression of NKCC1 restored intracellular chloride concentration and $GABA_AR$-mediated inhibition in trisomic neurons *in vitro*. Most importantly, AAV-mediated neuron-specific NKCC1 knockdown *in vivo* in the hippocampus of adult Ts65Dn animals rescued behavioral performance on different learning and memory tests at levels undistinguishable from those of WT mice. These findings indicate that NKCC1 upregulation drives intracellular chloride accumulation and depolarizing $GABA_AR$-signaling in trisomic cells, leading to behavioral impairments in DS mice. Moreover, our study identifies a new molecular target for treatments aimed at rescuing cognitive disabilities in individuals with DS.

Disclosures: A. Contestabile: None. **M. Parrini:** None. **S. Naskar:** None. **M. Alberti:** None. **M. Nanni:** None. **G. Ronzitti:** None. **F. Mingozzi:** None. **L. Cancedda:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.04

Topic: A.07. Developmental Disorders

Support: NIH Grant MH113352
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Jordan's Guardian Angels
Roy J. Carver Charitable Trust

Title: Generation and characterization of mice harboring Jordan's syndrome alleles causing intellectual disability with autism

Authors: *R. A. MERRILL[1], C. JONG[2], Y. KONG[1], G. L. HEALEY[1], S. STRACK[3]; [2]Pharmacol., [1]Univ. of Iowa, Iowa City, IA; [3]Univ. Iowa Col. Med., Iowa City, IA

Abstract: BACKGROUND: Protein phosphatase 2A (PP2A) activity is essential for eukaryotic cells and is controlled through its many regulatory subunits. Mutations in regulatory subunits have been associated with a wide variety of human diseases from cancer to intellectual disability. To date, more than sixty individuals have been identified that have *de novo* mutations in the *PPP2R5D* gene which encodes the PP2A regulatory protein B'delta. The affected individuals'

symptoms vary but can include intellectual disability, language delay, autism spectrum disorder, and seizures. **METHODS:** The most common and severe disease-causing mutation in humans is the E198K charge-reversal mutation, and therefore, we generated a mouse harboring this mutation in *Ppp2r5d* using CRISPR-Cas9 gene editing at the University of Iowa Genome Editing Core Facility. **RESULTS:** Mice harboring one E198K allele are viable but are born below expected frequency with either parent being carrying the mutation. Additionally, these mice often die as juveniles and show craniofacial abnormalities including cranial bossing. We have examined the brain structures by MRI and CT scans and have begun to investigate changes in glucose regulation/uptake and metabolomics. **CONCLUSION:** Mice heterozygous for the *Ppp2r5d* E198K mutation (reflecting the condition of Jordan's Syndrome patients) have highly penetrant phenotypes and will likely represent faithful models for studying the human disease.

Disclosures: R.A. Merrill: None. **C. Jong:** None. **Y. Kong:** None. **G.L. Healey:** None. **S. Strack:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.05

Topic: A.07. Developmental Disorders

Support: Sanfilippo Children Foundation
National MPS Society

Title: Disease' mechanism and therapeutic targets for autism-like behavior in a mouse model of mucopolysaccharidosis type IIIA

Authors: *M. DE RISI[1], M. TUFANO[2], F. G. ALVINO[2], S. PULCRANO[3], G. C. BELLENCHI[3], E. MARROCCO[1], N. C. SORRENTINO[1], M. CAIAZZO[4], A. FRALDI[2], E. DE LEONIBUS[5,6];
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Abstract: Autistic-like symptoms, including stereotyped behaviors and changes in sociability, characterize many neuropsychiatric developmental disorders, including rare genetic diseases such as Mucopolysaccharidosis type IIIA (MPS-IIIA). MPS-IIIA is a neurodegenerative lysosomal storage disorder characterized by the deficiency of the enzyme sulfamidase, which leads to altered metabolism of heparan sulfate. In the early stage of the pathology, children with

MPS-IIIA show autistic- like behavioural symptoms (ALBSs); ALBSs in MPS-IIIA have dramatic impact on their life and are resistant to behavioural and classic antipsychotic therapies. The disease' mechanisms leading to ALBSs in MPS-IIIA remain unexplored. In this study, we identified endophenotypes of ALBSs in young male MPS-IIIA mice, including social interaction impairment, increased stereotyped behaviours and hyperactivity. We then found that the identified ALBSs are associated to increased expression of mesencephalic tyrosine hydroxylase (TH) positive neurons appearing early during development and followed by increased striatal DA content. These changes in TH expression can be reproduced in cellular models of the disease. Using different behavioral pharmacological approaches, we identified at least two compounds that can rescue ALBSs in MPS-IIIA. These findings identify for the first time a developmental deficit in DA expression leading to ALBSs in MPS-IIIA mice; this has high translational relevance not only for this rare pathology but also for dissecting possible disease' pathways leading to iatrogenic autism. This study is supported by Sanfilippo Children Foundation and National MPS Society.

Disclosures: **M. De Risi:** None. **M. Tufano:** None. **F.G. Alvino:** None. **S. Pulcrano:** None. **G.C. Bellenchi:** None. **E. Marrocco:** None. **N.C. Sorrentino:** None. **M. Caiazzo:** None. **A. Fraldi:** None. **E. De Leonibus:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.06

Topic: A.07. Developmental Disorders

Title: Impaired neocorticogenesis and glymphatic-mediated CSF flow in the new genetic rat model of neonatal hydrocephalus

Authors: *J. GOTO[1], S. EMMERT[1], E. IWASAWA[1], C. SHULA[1], D. LINDQUIST[2], F. MANGANO[1];
[1]Pediatric Neurosurg., [2]Radiology, Cincinnati Children's Hosp., Cincinnati, OH

Abstract: Children with hydrocephalus are often treated with cerebrospinal fluid (CSF) diversion surgeries. It is notable that the patients with ameliorated ventricular volume still suffer from cognitive and neuropsychological deficits and hypomyelination long after the surgery. However, the normal CSF circulation system supporting neonatal brain development is not well elucidated. Recently we generated a novel genetic rat model of hydrocephalus with motile cilia defects through the CRISPR-Cas9 genome editing system. In T2 weigh MRI, we found the *Ccdc39* mutant rats accumulate CSF in the subdural space over the dorsal frontal cortex along with the enlarged lateral ventricles by postnatal day 11. Interestingly, monocytes/macrophages recruitment were found in the inflamed subpial CSF space between the pia membrane and the

neuropil. The dorsal penetrating vessels are the active CSF circulation route through the glymphatic and the Virchow-Robin space. We found that significantly reduced glymphatic flow and impaired cortical neuronal cell maturation in the neonatal mutant brains. Together with the previous clinical findings indicating the motile cilia defects in the patients with the extra-axial CSF accumulation, our data suggest that the motile cilia function is involved the CSF circulation through the glymphatic system and normal neocorticogenesis in the neonatal brain.

Disclosures: **J. Goto:** None. **S. Emmert:** None. **E. Iwasawa:** None. **C. Shula:** None. **D. Lindquist:** None. **F. Mangano:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

Location: Room N228

Time: Wednesday, October 23, 2019, 8:00 AM - 10:15 AM

Presentation Number: 627.07

Topic: A.07. Developmental Disorders

Support: Foxg1 Foundation Australia

Title: Loss of mitochondrial protein interactors through mutation associated with FOXG1 syndrome

Authors: D. C. S. TAN[1,2], L. M. ITTNER[1,2], F. DELERUE[1,2];
[1]Dementia Res. Ctr., [2]Genome Editing Macquarie, Macquarie Univ., Sydney, Australia

Abstract: FOXG1 syndrome is a neuro-developmental disorder that affects the early development of the telencephalon leading to severe cortical impairments. Patients typically present with post-natal microcephaly, severe mental retardation, apraxia and seizures. The disease is associated with mutations in the *FOXG1* gene, which encodes a transcription factor of the forkhead family. Here we report a novel clinically relevant mutation of the FOXG1 gene, a single nucleotide deletion c.946del (p.Leu316Cysfs*10) resulting in the premature truncation of the FOXG1 protein. We hypothesized that truncation of the FOXG1 protein leads to loss of potential interacting partners that may contribute to the pathology. To uncover these interacting partners, we performed immunoprecipitation of the FOXG1 protein and its mutant form in Neuro-2a cells, followed by mass spectrometry on purified extracts. Our results revealed significant association of FOXG1 with mitochondrial proteins. Furthermore, protein truncation leads to the loss of interactions with some of these mitochondrial proteins. These findings provide new insights into the cellular pathomechanisms of FOXG1 syndrome and validate the mitochondrial dysfunction observed in FOXG1 syndrome cases. Consequently, these findings could lead to new avenues for therapeutic strategies that aim to abate the symptoms of the disease.

Disclosures: **D.C.S. Tan:** None. **L.M. Ittner:** None. **F. Delerue:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

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Presentation Number: 627.08

Topic: A.07. Developmental Disorders

Support: NIH Grant GM090122

Title: Prenatal ultrasound of movement coordination after mild maternal hyperthermia (low grade fever) predicts differences in attachment and impulsivity in guinea pigs

Authors: *G. A. KLEVEN, Y. ARGUMEDO, S. GANN;
Wright State Univ., Dayton, OH

Abstract: Despite known associations between maternal hyperthermia (MHT, or fever) and harmful outcomes such as autism, little is known about the specific developmental mechanisms. Furthermore, the ability to predict future deficits during the prenatal period is limited. We developed a noninvasive guinea pig model to test whether changes in fetal Interlimb Movement Synchrony (IMS, a measure of coordination), brought about by exposure to MHT, would predict postnatal outcomes. IAF hairless female guinea pigs were time mated to NIH multicolored males. Hairless females were used to facilitate ultrasound observations of fetal movement and were acclimated to all procedures prior to mating. Pregnant females were exposed for 15 min to either a body temperature bath (40 ºC) or an elevation of body temperature by 2 ºC on day 30 of a 70-day gestation. Each female provided 2 pregnancies, one for the MHT group and another as a control, in random order. Fetal behavior was recorded on digital video from weekly ultrasound visualizations of not more than 15 min duration. IMS was scored from multiple passes of the ultrasound video records. Postnatal testing of social separation from mother and siblings was hypothesized to detect deficits in social bonding (attachment) of the pup to the mother. Conversely, guinea pigs are neophobic (avoiding anything new), and a novel food presentation in a familiar open arena was designed to test reactivity to novel stimuli as well as assess any hyper- or hypo- activity. All pups were tested as pre-weanlings between postnatal days 16-18. Fetal behavior revealed deficits in IMS. Similarly, postnatal testing revealed pups exposed to MHT spent less time approaching their mother, suggesting differences in attachment. MHT pups also were faster in approaching a novel food, compared to control offspring. However, activity levels were not different between the test groups, suggesting the faster approach to the novel food in the MHT pups was not hyperactivity, but rather impulsivity. These results demonstrate that assessment of fetal coordination through IMS can predict postnatal deficits resulting from mild MHT.

Disclosures: **G.A. Kleven:** None. **Y. Argumedo:** None. **S. Gann:** None.

Nanosymposium

627. Genetics and Neural Mechanisms of Developmental Disorders

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Presentation Number: 627.09

Topic: A.07. Developmental Disorders

Support: NIH BD2K EB020403
NIHM RO1 MH085953

Title: Myelin and G-ratio imaging in 22q11.2 deletion syndrome: A pilot study

Authors: *J. VILLALON REINA[1], T. M. NIR[2], L. KUSHAN[4], C. E. BEARDEN[5], N. JAHANSHAD[3], P. M. THOMPSON[6];
[1]USC Imaging Genet. Ctr., Marina del Rey, CA; [2]Imaging and Genet. Center, Stevens Neuroimaging & Informatics Inst., [3]Imaging Genet. Ctr., USC, Marina Del Rey, CA; [4]Semel Inst. for Neurosci. and Human Behavior, Univ. of California Los Angeles, Los Angeles, CA; [5]Semel Inst. for Neurosci. and Human Behavior, UCLA, Los Angeles, CA; [6]Stevens Inst. for Neuroimaging & Informatics, Univ. of Southern California (USC), Marina Del Rey, CA

Abstract: Introduction. Myelin is an important component of the white matter (WM) that wraps axons and promotes efficient conduction of action potentials. The relationship between axonal diameter and myelin sheath thickness is established by the g-ratio, which is defined as g=r/R, where r is the axonal diameter and R is the full fiber diameter (axon plus myelin). G-ratio has been estimated in multiple imaging modalities, including magnetic resonance imaging (MRI)1. Here we use diffusion MRI (dMRI) and myelin mapping to estimate the g-ratio across the entire brain in individuals with 22q11.2 Deletion Syndrome (22q11DS) and compare them to healthy controls (HC). Methods. We studied 12 HC (21.6 years±12.1), and 16 people with 22q11DS (20.3 years±8.7). 22q11.2 diagnosis was confirmed via microarray. Multi-shell dMRI data were acquired with b=1500, 3000 s/mm2, which allowed for reconstruction of the intracellular volume fraction (ICVF)2. Myelin volume fraction (MVF) was calculated as the ratio of T1-weighted to T2-weighted maps3. G-ratio maps were calculated as in Stikov et al1. Images were corrected for distortions and registered to the IIT atlas4. We compared the g-ratio and the MVF between both groups with a percentile bootstrap method for M-estimators across 17 IIT skeletonized WM regions. Results. We found higher MVF, on average, in the 22q11DS group in the left and right uncinate fasciculus and in the right cingulum. We found a significantly lower g-ratio in 22q11DS in the right cingulum (see Table). Conclusions. Previous diffusion tensor (DTI) studies have reported elevated fractional anisotropy (FA) in large areas of the brain's WM in 22q11DS5. There is no current plausible biological explanation of this finding. Microstructural imaging methods may shed light on this question. Our pilot results suggest that higher FA may result

from compensatory myelination in 22q11DS; ongoing work in larger samples is needed to confirm this. *References:* [1] Stikov N, et al. Neuroimage 2015; 118: 397-405. [2] Tariq M, et al. Neuroimage 2016; 133: 207-223. [3] Glasser MF, et al. J Neurosci 2011; 31: 11597-11616. [4] Zhang S, Arfanakis K. Neuroimage 2018; 172: 40-50. [5] Jalbrzikowski M, et al. Frontiers in Behavioral Neuroscience. 2014; 8. doi:10.3389/fnbeh.2014.00393.

Table. Percentile bootstrap for onestep M-estimators. Comparing 22q11DS subjects and Controls

Region of Interest	**Myelin Volume Fraction**	**G-Ratio**
Left Uncinate	Est. diff= -0.016; p=0.05 CI= -0.03, -0.00009	Est.diff=0.00059; p=0.97CI=-0.01, 0.01
Right Uncinate	Est.diff=-0.018; p=0.049 CI=-0.036, -0.00019	Est.diff=-0.002; p=0.68CI=-0.013, 0.0085
Right Cingulum	Est.diff=-0.031; p=0.019 CI: -0.061, -0.0073	Est.diff=0.025; p=0.012CI=0.0061 0.051
α=0.05; number of bootstraps=2000.		

Disclosures: J. Villalon Reina: None. **T.M. Nir:** None. **L. Kushan:** None. **C.E. Bearden:** None. **N. Jahanshad:** None. **P.M. Thompson:** None.

Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 628.01

Topic: B.11. Glial Mechanisms

Title: FITSAR: A novel method to generate cell type-specific protein signatures in human Alzheimer's disease brain

Authors: *J. S. SADICK[1,2], L. CRAWFORD[2], H. C. CRAMER[2], C. FRANCK[2,3], S. A. LIDDELOW[1], E. M. DARLING[2];
[1]NYU Sch. of Med., New York, NY; [2]Brown Univ., Providence, RI; [3]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Resolving cell type-specific contributions to Alzheimer's disease (AD) pathology is critical as reduced synaptic density, altered neuronal firing, and neuronal death largely do not occur in response to cell-autonomous changes. However, the majority of work characterizing human AD samples has involved bulk brain regional isolates in which cell heterogeneity is not taken into account or has relied solely on gene expression to reflect functional phenotypes. **Here**

we present the first proteomic investigation to compare neurons and astrocytes isolated from human, post-mortem AD and aged-matched non-symptomatic brains to gain better understanding of their contributions to AD pathology. Initially, we attempted to predict cell type-specific contributions to AD through bioinformatic analysis of published bulk proteomic datasets. However, these predictions were limited, which gave us greater impetus to generate proteomic signatures from enriched cell populations. Therefore, we optimized FITSAR (**F**ormaldehyde-fixed **I**ntracellular **T**arget-**S**orted **A**ntigen **R**etrieval), a new technique to characterize proteins from cell type-specific enriched populations, for proteomics and found that FITSAR is equally powerful at detecting proteins in fresh and preserved tissues. Applying this technique to human post-mortem samples, we found that freezer storage, fixation after tissue dissociation, and disease pathology does not greatly alter the number or abundance of proteins detected from enriched cell populations. To emphasize the power of FITSAR, proteomics datasets were evaluated for AD-associated markers, highlighting expected and novel protein signatures with cell type-specific resolution. These findings presented us with several testable hypotheses, regarding AD risk factors, astrocyte reactivity, and aging, for future studies. Ultimately, the FITSAR method is a fast and cost-effective way to obtain cell population-specific proteomic datasets from fixed, immunolabeled, and sorted human brain samples. We anticipate future investigations can apply this method to gain nuanced information about proportional cell contributions in AD and other diseases complicated by cell heterogeneity.

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Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 628.02

Topic: B.11. Glial Mechanisms

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Research to Prevent Blindness
Felix and Carmen Sabates Missouri Endowed Chair in Vision Research

Title: A novel druggable mechanism of action of cellular stress in astrocytes as a target for glioprotection

Authors: *P. KOULEN, J. C. MEANS, A. A. LOPEZ;
Univ. of Missouri Kansas City, Kansas City, MO

Abstract: Despite an improved understanding of optic nerve head (ONH) anatomy and function, particularly in the context of glaucoma-mediated tissue remodeling, contributions of ONH astrocytes (ONHA) to optic nerve damage remain to be defined in more detail. Exposure of ONHAs to oxidative stress can contribute to ONHA activation, axon damage and additional hallmarks of glaucoma. Insights in the mechanisms underlying oxidative stress-mediated damage to ONHAs can form the basis for strategies to protect ONHAs and thereby for advances towards slowing or preventing the progression of glaucoma and related disorders. Using our standardized protocols for the isolation and culture of primary adult rat ONHAs and for the assessment of their viability, we tested the hypothesis that ONHAs respond to oxidative stress with altered processing of tau protein and caspase activation as key elements of cellular degeneration. To this end, we exposed cells to oxidative stress using *tert*-butyl hydroperoxide (*t*BHP) modeling extracellular oxidative stress as it occurs in the retina and ONH. We combined this model with an intervention approach, pre-treatment of ONHAs with 17β-estradiol (E2), a steroid hormone with neuroprotective and antioxidant functions in the central nervous system. Exposure of ONHAs to *t*BHP-mediated oxidative stress resulted in significantly increased activation of caspase-3, dephosphorylation of tau at Ser^{422}, and a significant increase in tau protein cleavage associated with the formation of neurofibrillary tangles. Pretreatment of ONHAs with E2 prevented oxidative stress-mediated increases in all three of these measures of cellular degeneration and cell death. We conclude from these data sets that oxidative stress triggers distinct pathways of cellular damage, which potentially result in decreased cell function and can ultimately activate apoptosis in ONHAs. In addition, we provide experimental evidence for effective prevention of the activation of these degenerative signaling pathways by E2 not only as a potentially therapeutically relevant compound, but also as a means to accelerate the discovery of biologically relevant target engagement relevant for the protection of ONHA function and for the prevention of neurodegeneration in glaucoma and related disorders of the CNS.

Disclosures: P. Koulen: None. **J.C. Means:** None. **A.A. Lopez:** None.

Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

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Presentation Number: 628.03

Topic: B.11. Glial Mechanisms

Support: HK RGC GRF #16103317
HK RGC GRF # 16100718
US AARF (AARF-17-531566)

Title: WNT downstream signalling modulates the neurotrophic versus neurotoxic fates of astrocytes: Implications in the Alzheimer’s disease (AD)

Authors: *H.-M. CHOW[1], K.-Y. CHENG[2], H.-L. HUNG[3];
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Abstract: WNT signalling is crucial for normal brain functioning and impaired signalling is associated with late onset AD. Currently, the majority of studies on WNT signalling are focused on neurons with much less known about its potential roles in non-neuronal cells such as astrocytes. We have been drawn to the astrocyte population both because they offer primary metabolic support to neurons and because they are subjected to the same AD microenvironment during disease progression. We identified that WNT normally regulates fuel metabolism in astrocytes and altered downstream signaling axis modulates their cellular physiology. Our findings suggest that the WNT-LRP6-mTOR-AKT axis, but not the canonical β-catenin-dependent axis, is the primary WNT pathway supporting astro-glia metabolism. Impairment of that by direct knockdown of LRP6 co-receptor switches WNT signaling from the mTOR-AKT signaling to the Ca2+-PCP-NFAT and JNK-AP1 axes. This initiates a pro-inflammatory reprogramming of astrocytes, thus inducing toxicity to neurons. Similar reprogramming is also induced by DKK1, a WNT secreted antagonist that is known to be upregulated in human AD. This work offers new insights on how WNT signaling modulates astrocyte physiology as well as its role in the pathogenesis of AD.

Disclosures: H. Chow: None. **K. Cheng:** None. **H. Hung:** None.

Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 628.04

Topic: B.11. Glial Mechanisms

Support: Minnesota Partnership for Biotechnology and Medical Genomics (MNP #17. 16)

Title: Programmable modulation of extracellular vesicles

Authors: *H.-L. WANG[1], Y. WANG[1], R. MELVIN[2], L. BEMIS[2], G. WORRELL[1];
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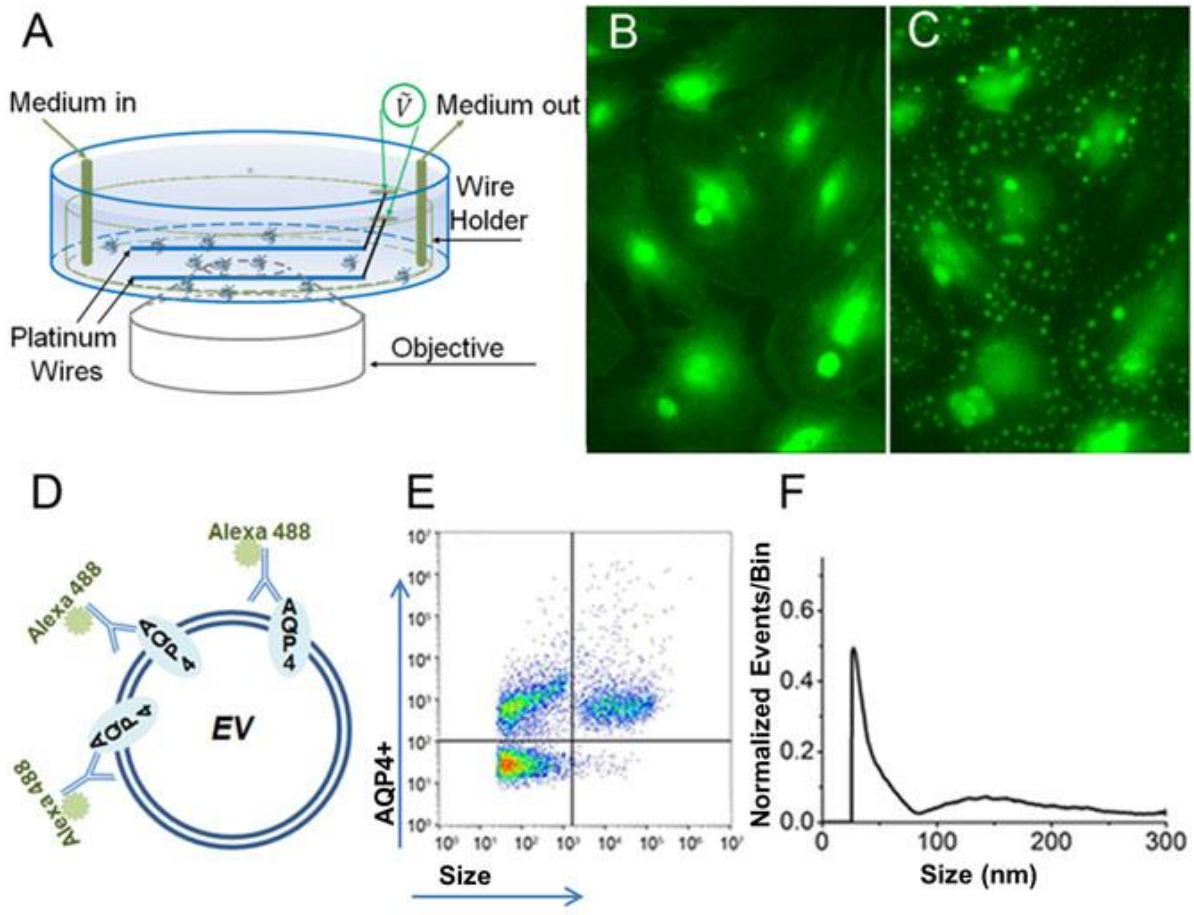
Abstract: Every living cell releases extracellular vesicles (EVs) that are critical for cellular signaling and a wide range of biological functions. The potential diagnostic and therapeutic applications of EVs are well recognized, and rapidly expanding. While a complete understanding of the molecular mechanisms underpinning EVs release remains elusive, here we demonstrate a novel method for programmable control of the release of EVs and their cargo using external

electric fields. We applied electric field at three different frequencies (low, intermediate and high) to astrocyte cultures through a custom rig designed to create uniform fields over the astrocytes with continuous fluid exchange to collect EVs. As proof of principle, we use cultured rat astrocytes to demonstrate how the frequency of external electrical stimulation selectively modulates EV release, their surface proteins, and microRNA profiles. This method could broadly impact biological science and medical applications. First, it raises an interesting question of how endogenous electrical activity could modulate EV production. In fact, these frequencies fall into the three typical endogenous brainwave oscillation frequencies recorded with intracranial electroencephalography, delta (0. 5 - 4 Hz), beta-gamma (12 - 30 Hz) and ripple (100 - 200 Hz). Second, it provides a novel mechanism for tuning therapeutic electrical stimulation in treating several neurological and other diseases including brain disorders. Third, it provides a new way to generate EVs carrying desired cargos by tuning electrical stimulation parameters. Unlike chemical methods for creating EVs, electrical stimulation is a clean physical method with adjustable parameters including oscillation frequency, field strength and waveform.



Disclosures: **H. Wang:** None. **Y. Wang:** None. **G. Worrell:** None. **R. Melvin:** None. **L. Bemis:** None.

Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 628.05

Topic: B.11. Glial Mechanisms

Title: Astrocytic proBDNF and tonic GABA distinguish active versus reactive astrocytes in hippocampus

Authors: *H. CHUN[1], H. AN[1], J. LIM[1], J. WOO[2], J. LEE[3], H. RYU[4], C. J. LEE[1];
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Abstract: Astrocytes are the most abundant cell type in the brain and they make close contacts with neurons and blood vessels. They respond dynamically to various environmental stimuli and change their morphological and functional properties. Both physiological and pathological stimuli can induce versatile changes in astrocytes, as this phenomenon is referred to as ‘astrocytic plasticity’. However, the molecular and cellular mechanisms of astrocytic plasticity in response to various stimuli remain elusive, except for the presence of hypertrophy, a conspicuous structural change which is frequently observed in activated or reactive astrocytes. Here, we investigated differential characteristics of astrocytic plasticity in a stimulus-dependent manner. Strikingly, a stab wound brain injury lead to hypertrophy of astrocytes accompanied by increased GABA expression and tonic GABA release in mouse CA1 hippocampus. In contrast, the mice experiencing enriched environment exhibited astrocytic hypertrophy with enhanced proBDNF immunoreactivity but without GABA signal. Based on the results, we define proBDNF-positive/GABA-negative hypertrophic astrocytes as ‘active’ astrocytes and GABA-positive hypertrophic astrocytes as ‘reactive’ astrocytes, respectively. We propose for the first time that astrocytic proBDNF can be a *bona fide* molecular marker of the active astrocytes, which are distinct from the reactive astrocytes which show hypertrophy but with aberrant GABA.

Disclosures: H. Chun: None. **H. An:** None. **J. Lim:** None. **J. Woo:** None. **J. Lee:** None. **H. Ryu:** None. **C.J. Lee:** None.

Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 628.06

Topic: B.11. Glial Mechanisms

Support: 1R01DA041513
5T32DA016176

Title: Aberrant neuroglial coupling the in PFC contributes to cocaine-induced cognitive deficits

Authors: *R. D. COLE, P. I. ORTINSKI;
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Abstract: The prefrontal cortex (PFC) is crucial for updating and integrating strategies to maintain goal-directed behavior. Repeated cocaine use induces maladaptive neuroadaptations in the PFC and reduces decision-making abilities. While glutamatergic (Glu) signaling between PFC neurons has been a focus of many studies, the influence of astrocytic Glu on cocaine-induced neuroadaptations is not as clear. Glu released from astrocytes prominently targets extrasynaptic NMDA receptors (eNMDAR), generating a characteristic slow inward current (SIC) in nearby neurons. The present study characterized astrocytic contributions to drug-induced neuronal plasticity and associated PFC cognitive deficits under conditions of reduced eNMDAR function. Reduction of eNMDAR signaling was achieved by infusion of shRNA targeting an eNMDA anchoring protein, GIAP-interacting protein C-terminus 1 (GIPC1), into the PFC of Sprague-Dawley rats. Controls received an infusion of non-complementary shRNA (NC). Rats were trained to self-administer (SA) cocaine on a long access schedule (6h) for 10 days and paired with saline-yoked controls. All rats were also trained on an operant-based cognitive flexibility task to examine their decision-making abilities 24h after cocaine SA. After behavioral testing, brains were extracted and prepared for whole-cell patch clamp electrophysiology. Cocaine SA significantly increased the frequency of neuroglial SIC events in cocaine-NC animals compared to yoke-GIPC1 and yoke-NC rats ($p<0.05$). Conversely, GIPC1 knock-down attenuated SIC frequency in cocaine treated animals ($p<0.05$) to non-cocaine levels. No significant differences were found in spontaneous excitatory postsynaptic current amplitude or frequency (both $p>0.79$) regardless of group. When examining decision-making, cocaine SA was associated with significant impairment in the ability to adopt a new behavioral strategy in cocaine-NC rats ($p<0.01$). Further examination of these data revealed that cocaine-NC rats committed significantly more errors compared to all other groups ($p<0.05$). These cognitive deficits were not observed in cocaine-GIPC1 group ($p=0.20$). Taken together, these results indicate that cocaine SA increases PFC neuroglial coupling and results in decision-making impairments. Attenuation of eNMDAR signaling normalizes neuronal sensitivity to astrocytic glutamate and prevents cocaine-induced cognitive deficits. Etiology of cocaine use disorder may therefore involve aberrant astrocyte-neuron interactions in the PFC.

Disclosures: R.D. Cole: None. **P.I. Ortinski:** None.

Nanosymposium

628. Reactive Astrocytes: Molecular Mechanisms and Disease Models

Location: Room S405

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 628.07

Topic: B.11. Glial Mechanisms

Support: FAPERJ
CNPq
CAPES
BNDES
INNT

Title: Characterization of functional astrogliosis using human induced pluripotent stem cells-derived astrocytes

Authors: *P. TRINDADE[1,2], E. C. LOIOLA[2], P. F. LEDUR[2], J. D. SALERNO[2,3], L. R. Q. SOUZA[2], P. L. CARDOZO[4], S. DEVALLE[2], I. M. ORNELAS[2], F. M. RIBEIRO[4], A. M. VENTURA[5], D. P. GELAIN[6], L. O. PORCIÚNCULA[6], S. K. REHEN[2,3];
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Abstract: Astrogliosis has been implicated in several neurodegenerative and neuropsychiatric disorders. However, most mechanisms underlying astrogliosis were described using animal models, which fail to fully reproduce the complexity of human cell signaling. Here, we report a model to study astrogliosis in a dish using human induced pluripotent stem cells (iPSC)-derived astrocytes, which replicates several aspects of reactive astrocytes. We analyzed major events related to the time course of astrogliosis by measuring nuclear translocation of NF-kB, secretion of cytokines and changes in morphological phenotypes of human iPSC-derived astrocytes. These cells responded to TNF-α by promoting NF-kB nuclear translocation. Additionally, inflammation-related cytokines were found increased following TNF-α stimulation. Some of these cytokines showed increased gene expression according to qPCR measurements. Cells exposed to TNF-α also exhibited typical phenotypes of astrogliosis, such as an increase in vimentin and GFAP immunolabeling, changes of the cell aspect ratio and the shrinkage of nuclei. Moreover, a systematic decrease on d-[^{3}H]aspartate uptake along the time course of astrogliosis was observed. Taken together, our results indicate that iPSC-derived astrocytes successfully reproduce major hallmarks of astrogliosis in culture and also confirm that the glial glutamate/aspartate uptake system is disrupted in human activated astrocytes. Thus, the model of human astrogliosis described here may contribute to better understand inflammatory components of human neurological disorders and potentially serve as a tool for drug screening.

Disclosures: P. Trindade: None. **E.C. Loiola:** None. **P.F. Ledur:** None. **J.D. Salerno:** None. **L.R.Q. Souza:** None. **P.L. Cardozo:** None. **S. Devalle:** None. **I.M. Ornelas:** None. **F.M. Ribeiro:** None. **A.M. Ventura:** None. **D.P. Gelain:** None. **L.O. Porciúncula:** None. **S.K. Rehen:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.01

Topic: C.03. Parkinson's Disease

Support: NIH AG063373
NIH T32EB006359

Title: Biodegradable pH-responsive nanoparticle acidify lysosomes and modulate autophagy in PC-12 cells

Authors: *J. ZENG[1], A. MARTIN[2], O. SHIRIHAI[3], X. HAN[1], M. GRINSTAFF[2];
[1]Biomed. Engin., [2]Boston Univ., Boston, MA; [3]UCLA, Los Angeles, CA

Abstract: We have developed a novel pH-responsive and acidifying nanoparticle (acNP) that restores the pH of compromised lysosomes to rescue autophagic flux and cellular function in neural PC-12 cells under exposure to varying concentrations of either 1-methyl-4-phenylpyridinium (MPP+) mitochondria toxin or 6-hydroxydopamine (6-OHDA). Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world, with about 60,000 new cases identified each year. The burden of PD had risen every year with an aging population. PD results mainly from the death of dopaminergic neurons in the substantia nigra pas compacta, due to accumulation of toxic protein aggregates such as alpha synuclein (a-syn) within Lewy bodies and neurites that are unable to be degraded. Recent studies in both cellular and mouse models of PD have indicated that perturbations in macro-autophagy, a critical quality control process that mediates the degradation of a-syn, play a role in PD pathogenesis. Impairment in lysosomal acidity and function has been reported to result in a-syn aggregates accumulation, and compromises its degradation. Therefore, targeting the restoration of lysosomal acidity signify a new target for therapeutic development. Although some studies have demonstrated that genetic restoration of autophagy can inhibit PD development, no effective therapeutic approach has been developed to date. In this study, we designed an acidic nanoparticle containing caged acid which can be released upon degradation under slight pH changes to enable controlled acidification of the impaired PC-12 lysosomes under MPP+ and 6-OHDA insults. The non-cytotoxic acNPs display high localization in the lysosomes of PC-12 cells, rescue MPP+ and 6-OHDA induced PC-12 cell death, restore lysosomal acidity and decrease the accumulation of autophagic proteins LC3II and p62 levels, indicating an overall rescue of autophagic flux. These results established a primary causative role of impaired lysosomal acidification on the de-regulation of autophagic flux and cellular function in PC-12 cells, and the acNPs may pave the way for nanoparticles as a novel treatment option for neurodegenerative diseases in which lysosomal acidity is impaired, such as PD and Alzheimer's disease.

Disclosures: J. Zeng: None. **A. Martin:** None. **O. Shirihai:** None. **X. Han:** None. **M. Grinstaff:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.02

Topic: C.03. Parkinson's Disease

Support: NIA Intramural Research Program

Title: A mouse model with an endogenous mutation in DNAJC6 with motor phenotypes links altered clathrin trafficking to Parkinson's disease

Authors: D. A. ROOSEN[1], N. LANDECK[2], M. CONTI[2], N. SMITH[3], S. SAEZ-ATIENZAR[2], J. DING[2], J. DU HOFFMANN[4], A. BEILINA[2], R. KUMARAN[2], A. KAGANOVICH[2], L. BONET-PONCE[2], C. BLECK[5], C. LIU[5], J. BONIFACINO[6], Y. LI[7], P. LEWIS[8], ***M. R. COOKSON**[1];
[1]Natl. Inst. Aging, NIH, Bethesda, MD; [2]Natl. Inst. on Aging, Bethesda, MD; [3]Univ. of Nebraska Lincoln, Lincoln, NE; [4]Natl. Inst. of Mental Hlth., Bethesda, MD; [5]Natl. Heart Lung and Blood Inst., Bethesda, MD; [6]Natl. Inst. of Child Hlth. and Develop., Bethesda, MD; [7]Natl. Inst. of Neurolog. Dis. and Stroke, Bethesda, MD; [8]Univ. of Reading, Reading, United Kingdom

Abstract: Parkinsons disease (PD) is a common neurodegenerative motor disorder, characterized by neuropathological lesions in the nigrostriatal pathway. While most cases of PD are sporadic in nature, inherited PD-like syndromes can be caused by mutations in several genes. Multiple loss of function mutations in the gene *DNAJC6*, which encodes the protein auxilin, have been found to cause an aggressive form of young onset PD. Wild type auxilin is known to play a role in clathrin trafficking, which is crucial for cellular function in all eukaryotes and plays a specialized role in synaptic transmission in higher organisms. Clathrin-coated vesicles (CCVs) mediate selective transport of cargo from the plasma membrane and trans-Golgi network to intracellular destinations. Auxilin is the major neuronal CCV uncoating protein required for successful delivery of cargo to its destination compartments. How mutations in DNAJC6/auxilin cause PD is currently not understood.
To address this question, we generated a novel mouse model carrying a pathogenic Auxilin mutation knocked into the mouse genome. When bred to homozygosity, this mutation induced neurological phenotypes that phenocopy clinical features seen in patients, including motor impairments reminiscent of bradykinesia and gait problems. Mapping the interactome of Auxilin confirmed clathrin and clathrin adaptor protein interactions relevant for synaptic function, but also novel Golgi-resident interactors. Furthermore, transcriptome analysis of mutant Auxilin neurons revealed the activation of the Golgi stress response. Impaired clathrin trafficking in R857G Auxilin mice, both at the synapse and the Golgi, was found to result in neuropathological lesions in the nigrostriatal pathway. Collectively, these results novel insights for PD pathogenesis

in Auxilin mutation carriers, using a model that replicates the endogenous context of the mutations. In addition, these data reinforce an important role for clathrin trafficking in PD.

Disclosures: **D.A. Roosen:** None. **N. Landeck:** None. **M. Conti:** None. **N. Smith:** None. **S. Saez-Atienzar:** None. **J. Ding:** None. **J. du Hoffmann:** None. **A. Beilina:** None. **R. Kumaran:** None. **A. Kaganovich:** None. **L. Bonet-Ponce:** None. **C. Bleck:** None. **C. Liu:** None. **J. Bonifacino:** None. **Y. Li:** None. **P. Lewis:** None. **M.R. Cookson:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.03

Topic: C.03. Parkinson’s Disease

Support: VA Grant BX003249
NIH Grant NS105774

Title: c-Abl activation and cell death caused by alpha-synuclein aggregates are mediated by oxidatives stress and blocked by n-acetyl cysteine

Authors: *S. GHOSH[1], S. WON[1], N. J. M. BUTLER[1], R. FONG[1], C. WONG[1], L. WU[1], J. SANCHEZ[1], J. WANG[1], J. PAN[1], F. P. MANFREDSSON[2], R. A. SWANSON[1];
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Michigan State Univ., Grand Rapids, MI

Abstract: Cell death induced by intracellular alpha-synuclein aggregates is mediated in part by activation of the protein kinase c-Abl. c-Abl activation can be initiated directly or indirectly through reactive oxygen species. Here we show that alpha-synuclein aggregates induce c-Abl activation by an oxidant stress mechanism. In primary neuron cultures, aggregates induced by exposure to preformed alpha-synuclein fibrils (PFFs) produced lipid oxidation, c-Abl activation, and cell death. All of these effects were attenuated by co-incubation with N-acetyl cysteine (NAC), a cysteine pro-drug that supports neuronal glutathione synthesis. Neuronal exposure to hydrogen peroxide likewise led to c-Abl activation and was prevented by NAC. A similar pattern was observed using two mouse models of Parkinson’s disease; AAV-mediated expression of human alpha-synuclein, and injection of PFFs into the substantia nigra. In both models, c-Abl activation and oxidative injury were observed in regions that developed alpha-synuclein aggregates, and in both models these effects were attenuated by oral NAC delivery. Last, a transgenic mouse strain with deficient neuronal glutathione levels and elevated basal levels of neuronal oxidative stress (EAAT3$^{-/-}$ mouse) showed c-Abl activation in neurons, and this too was reduced by oral NAC treatment. Taken together, these findings indicate that alpha-synuclein

aggregates cause c-Abl activation by an oxidant stress mechanism, and that this process can be blocked by NAC.

Disclosures: S. Ghosh: None. **S. Won:** None. **N.J.M. Butler:** None. **R. Fong:** None. **C. Wong:** None. **L. Wu:** None. **J. Sanchez:** None. **J. Wang:** None. **J. Pan:** None. **F.P. Manfredsson:** None. **R.A. Swanson:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.04

Topic: C.03. Parkinson’s Disease

Title: The dopamine oxidation product HOCD may account for the dopaminergic selectivity of both Parkinsonism and manganism

Authors: P. MARWAH, C. ISSA, M. QURESHI, *D. NJUS;
Biol. Sci., Wayne State Univ., Detroit, MI

Abstract: Parkinson’s disease and manganism cause similar symptoms because both selectively target dopaminergic neurons. We have discovered a dopamine derivative, hypochlorite-oxidized cysteinyl-dopamine (HOCD), that is a potent redox cycler and may contribute to the oxidative stress observed in Parkinson’s disease. HOCD is formed when cysteinyl-dopamine, the principal oxidation product of dopamine *in vivo*, is exposed to hypochlorite. Hypochlorite is produced by the enzyme myeloperoxidase, which is reportedly elevated in Parkinson’s disease. Now we report that the two-equivalent redox cycling of HOCD is greatly amplified by $MnCl_2$, suggesting that HOCD may also contribute to the movement disorders associated with chronic manganese poisoning or manganism. Mn at micromolar concentrations accelerates the reoxidation of HOCD reduced by dithiothreitol, H_2 or NADH and NADH-quinone oxidoreductase (NQO1). Other metal ions including Cu, Fe, Co, and Zn do not have this effect. We suggest that HOCD may occur naturally at low concentrations in the substantia nigra. Its deleterious action may be elicited by complexing to Mn causing manganism or by an abnormal increase in its concentration contributing to Parkinson’s disease.

Disclosures: P. Marwah: None. **C. Issa:** None. **M. Qureshi:** None. **D. Njus:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

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Presentation Number: 629.05

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS086890

Title: S-nitrosylation of p62 attenuates autophagic flux in models of Parkinson's disease

Authors: *C.-K. OH[1], T. NAKAMURA[1], S. A. LIPTON[2];
[1]Neurosci. Translational Center, Departments of Mol. Med. and Neurosci., The Scripps Res. Inst., La Jolla, CA; [2]Neurosci. Translational Center, Departments of Mol. Med. and Neurosci., The Scripps Res. Inst. and UC San Diego, La Jolla, CA

Abstract: Autophagy is the major intracellular degradation system for removal of damaged organelles and abnormal aggregated proteins. Emerging evidence suggests that impaired autophagy contributes to the pathogenesis of neurodegenerative disorders, including Parkinson's disease (PD), via accumulation of abnormally aggregated proteins. Another important hallmark of neurodegenerative diseases includes excessive generation of reactive oxygen and nitrogen species (ROS/RNS), such as nitric oxide (NO), potentially accelerating neuronal injury. Along these lines, our group pioneered studies of protein S-nitrosylation, representing NO-mediated posttranslational modification of a critical cysteine residue on a target protein. We and others have shown that aberrant S-nitrosylation mediates, at least in part, the neurotoxic effects of NO. However, how protein S-nitrosylation affects autophagy remained incompletely understood. Here, we show in various experimental models of PD, including hiPSC-derived A9-type dopaminergic neurons (hiPSC-DA), that S-nitrosylation of p62 (SNO-p62) inhibits autophagic flux. hiPSC-DA bearing the A53T mutation in α-synuclein and the brains of transgenic mice overexpressing human α-synuclein under the Thy1 promoter both manifested increased SNO-p62. Moreover, isogenic wild-type (WT) hiPSC-DA exposed to rotenone also showed increased S-nitrosylation of p62. p62 normally functions as an autophagic adapter protein through direct interaction with LC3 and polyubiquitin, facilitating autophagic/lysosomal degradation of ubiquitinated proteins/organelles. Intriguingly, we found that S-nitrosylation of p62 increased its binding to LC3 and that mutation of the SNO-site to alanine (C331A) also enhanced interaction between p62 and LC3. Hence, the non-nitrosylatable p62 mutant mimicked the effect of S-nitrosylation. Next, using CRISPR/Cas9 we generated a stable SH-SY5Y DA neural cell line with the p62(C331A) non-nitrosylatable mutation. These SH-SY5Y p62(C331A) cells manifested drastically attenuated autophagic flux compared to WT cells. Taken together, our findings are consistent with the notion that aberrant S-nitrosylation of p62 decreases autophagic flux, contributing to accumulation of aggregated proteins and damaged organelles. We speculate that preventing formation of SNO-p62 may be therapeutic in PD and other neurodegenerative diseases associated with nitrosative stress-induced autophagic defects.

Disclosures: C. Oh: None. **T. Nakamura:** None. **S.A. Lipton:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

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Presentation Number: 629.06

Topic: C.03. Parkinson's Disease

Support: NIH grant NS105774
VA grant BX003249

Title: Oxidative injury and DNA damage are mediated by the interaction of alpha-synuclein aggregates with metal ions

Authors: *E. CASTILLO, J. WANG, R. SWANSON;
Univ. of California, San Francisco, San Francisco, CA

Abstract: Aggregates of alpha-synuclein contribute to the pathogenesis of Parkinson's disease (PD). In addition, several studies have shown production of oxidative stress in affected neurons in human PD and animal models of PD. Evidence also indicates disturbances of metal homeostasis in the substantia nigra of PD subjects, and treatment with a metal chelator (deferiprone) is currently under clinical investigation. Nevertheless, the mechanistic relationships between alpha-synuclein aggregates, oxidative injury, and metal dys-homeostasis remain uncertain. To identify potential mechanisms linking these pathologies we treated primary neurons and differentiated SH-SY5Y cells with pre-formed alpha-synuclein fibrils to produce intracellular alpha-synuclein aggregates. Intracellular aggregates were detected at the cellular level by proximity ligation assay and by western blotting in the triton-insoluble protein fraction. Oxidative stress and DNA damage were observed in cells containing aggregates, and not observed in cells that overexpressed alpha-synuclein but did not contain aggregates. Crucially, the oxidative injury and DNA damage were substantially reduced by the iron chelator deferoxamine, and completely blocked by the copper chelator triethylenetetramine. These findings suggesting that a direct interaction with iron and/or copper ions may be required for the cytotoxic effects of alpha-synuclein aggregates.

Disclosures: E. Castillo: None. **J. Wang:** None. **R. Swanson:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

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Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.07

Topic: C.03. Parkinson’s Disease

Support: Fundación Tatiana Pérez de Guzmán el Bueno

Title: Immunogenic CD8+ T cell-mediated neuronal death as an initiator and progressor of Parkinson's disease: A histological study of T cell subsets including iLBD post-mortem tissue

Authors: *J. GALIANO-LANDEIRA, A. TORRA, C. PARIENTE, M. VILA, J. BOVÉ; Vall d'Hebron Res. Inst., Barcelona, Spain

Abstract: Parkinson’s disease (PD) is characterized by a progressive loss of midbrain dopaminergic neurons, presence of α-synuclein enriched Lewy bodies and chronic neuroinflammation. Mounting evidence suggests that both innate and adaptive immune systems play a relevant role in the pathogenesis of the disease. Activated microglia surrounding dopaminergic neurons have been observed and appeared to correlate with deposits of α-synuclein. Later on, it was reported an increase of the number of T cells in the substantia nigra *pars compacta* (SN*pc*) of PD patients, but a phenotypic characterization of the different subpopulations of CD4+ and CD8+ T cells in the brain has never been performed. To shed some light on the role of the adaptive immune response on the onset and progression of PD, and its interrelation with microgliosis and α-synucleinopathy, we have assessed all these parameters in healthy controls, incidental Lewy Body Disease (iLBD) (considered to be a preclinical stage of PD) and PD post-mortem SN*pc*. While we detected an increase of CD8+ T cells density in the parenchyma of PD cases that positively correlated with neuronal death, no changes of CD4+ T lymphocytes were observed. In all three groups, a high percentage of CD8+ T cells expressed a residence phenotype and were interferon-ϒ and/or granzyme positive. For the first time we demonstrate that CD8+ T cell infiltration is an early event of the disease since we observed not only an increase of their numbers in iLBD cases but also an increase of their lytic capacity. Overall, our results suggest that CD8+ T cells mediate an extremely early immunogenic neuronal death that initiates and makes progress Parkinson’s disease.

Disclosures: J. Galiano-Landeira: None. **A. Torra:** None. **C. Pariente:** None. **M. Vila:** None. **J. Bové:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

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Presentation Number: 629.08

Topic: C.03. Parkinson’s Disease

Support: CIHR Grant PJT148736

Title: Endocytic trafficking of alpha-synuclein fibrils through the lysosomal pathway and the induction of cytoplasmic pS129 aggregates

Authors: L. RODRIGUEZ, F. SAMUEL, ***A. TANDON**;
CRND, Univ. of Toronto, Toronto, ON, Canada

Abstract: In Parkinson's disease, neuronal inclusions composed of aggregated α-synuclein (α-syn) spread through the brain following a stereotypic pattern, in support of the hypothesis that neuron-to-neuron transfer is critical for the propagation of Lewy pathology. Recent studies have shown that misfolded α-syn can be both internalized and released by different cell types including neurons however, the mechanism for the uptake and the consequences to endogenous α-syn completely understood.
We investigated the cellular mechanisms underlying α-syn fibril internalization in mouse and human neurons, and the consequences on endogenous cytoplasmic α-syn. Exogenous, single-fluorophore labelled α-syn fibrils were internalized by endocytosis and trafficked to late endosomal compartments and to multivesicular bodies (MVBs), which may serve as an intermediate sorting compartment to direct α-syn towards lysosomes for degradation or to the plasma membrane for release. In primary neurons, fibrils were very slowly degraded as they were still detectable in late endosomes/MVBs 14 days post-treatment. α-Syn fibrils induced an abnormal endosome morphology and enlarged Lamp1-positive MVB/lysosomes, consistent with aberrant p62 accumulation and impaired autophagic degradation. Moreover, 7-14 days after exposure to fibrils, we observed a profound time-dependent appearance of pS129-positive aggregates in axons and dendrites and in large perinuclear inclusions.
These results suggest that endocytosed α-syn fibrils are poorly degraded by neuronal protein degradation pathways and induce significant post-translational and structural changes to cytoplasmic α-syn.

Disclosures: L. Rodriguez: None. **F. Samuel:** None. **A. Tandon:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.09

Topic: C.03. Parkinson’s Disease

Support: R01 NS076054 / Project 60047407

Title: Misregulation of mitochondria - lysosome contact sites in mutant GBA (beta-glucocerebrosidase) Parkinson's patient neurons

Authors: *S. KIM, Y. C. WONG, L. F. BURBULLA, D. KRAINC;
Dept. of Neurol., Northwestern Univ., Chicago, IL

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder and has been linked to defects in both mitochondrial and lysosomal function. However, while mitochondria and lysosomes are critical organelles for maintaining neuronal homeostasis, how their dynamics are bidirectionally regulated in neurons is still not well understood. Our lab recently identified the dynamic formation of inter-organelle mitochondria-lysosome contact sites in non-neuronal cells which are essential for regulating the network dynamics of both mitochondria and lysosomes (*Wong et al., Nature 2018*). However, the role of mitochondria-lysosome contact sites in human neurons, as well as their contribution to Parkinson's disease pathogenesis has not been previously studied. Using human iPSC-derived dopaminergic neurons, we found that mitochondria-lysosome contact sites dynamically form in the cell body, axon and dendrites of human neurons. Interestingly, mitochondria-lysosome contact sites are potentially affected by lysosomal enzymes, as reduced activity of the lysosomal enzyme GBA (β-glucocerebrosidase) disrupts lysosomal dynamics contributing to defective mitochondria-lysosome contact site formation. Moreover, heterozygous GBA mutations in familial Parkinson's disease patient neurons exhibit dysfunctional mitochondria-lysosome contact dynamics, resulting in disrupted mitochondrial dynamics in both the axon and cell body. Together, these findings may advance our understanding of fundamental biology underlying the interplay between mitochondria and lysosomes in neurons, and provide important insights into disease pathogenesis in Parkinson's disease.

Disclosures: S. Kim: None. **Y.C. Wong:** None. **L.F. Burbulla:** None. **D. Krainc:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.10

Topic: C.03. Parkinson's Disease

Support: NINDS: R01NS109157
Michael J. Fox Foundation (grant ID 12158.01)

Title: The role of glycosphingolipids in the progression of synucleinopathies *in vivo*

Authors: *S. AIVAZIDIS, K. FREDRIKSEN, F. ZUNKE, E. GELYANA, J. MAZZULLI;
Ken and Ruth Davee Dept. of Neurol., Northwestern University, Feinberg Sch. of Med., Chicago, IL

Abstract: Parkinson’s disease (PD) is neurodegenerative movement disorder characterized pathologically by insoluble a-synuclein (a-syn) inclusions. Mutation of several genes involved in the autophagic/lysosomal protein degradation process are associated with impaired a-syn clearance and PD pathogenesis, indicating that perturbations in proteostasis contribute to disease. This relationship is best highlighted by genetic studies demonstrating that lysosomal *GBA1* mutations are the strongest risk factor for developing PD. The *GBA1* gene encodes the lysosomal glucocerebrosidase protein (GCase) that degrades glucosylceramide (GluCer) (a glycosphingolipid (GSL) that serves as an intermediate in glycolipid metabolism) to glucose and ceramide. *GBA1* defects result in GSL accumulation and lysosomal dysfunction. In addition to PD, homozygous *GBA1* mutations cause the rare lysosomal storage disorder, Gaucher Disease (GD), which can also be characterized by parkinsonism. Previous research from our lab has established that GSLs convert physiological a-syn into soluble, toxic oligomeric intermediates and pathological insoluble fibrils. We also showed that this process is reversible, since GSL reduction can decrease pathological a-syn species in patient-derived midbrain neurons from induced pluripotent stem cells (iPSn). Here, we examined this process *in vivo* using a pharmacological mouse model of GD, using the GCase inhibitor conduritol-beta-epoxide (CBE). We show that wild-type mice exhibit both physiological monomers and high molecular weight a-syn conformers. CBE injection of mice expressing wild-type *GBA1* induces GSL accumulation leading to the formation of toxic a-syn oligomers *in vivo*. GSL-induced pathological a-syn correlates with an elevation in microglial inflammatory marker Iba-1, suggesting that these species induce neural injury. Our studies indicate that GSL accumulation is sufficient to convert a-syn into toxic species *in vivo*, and suggest that reduction of GSLs will provide benefit in *GBA1*-PD through reduction of pathological a-syn.

Disclosures: S. Aivazidis: None. **K. Fredriksen:** None. **F. Zunke:** None. **E. Gelyana:** None. **J. Mazzulli:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lysosomal Therapeutics Inc..

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.11

Topic: C.03. Parkinson’s Disease

Support: Natural Science Foundation of Shandong Province of China ZR2018BC022

Title: Cdk5-mediated phosphorylation of TFEB prevents its nuclear translocation and inhibits autophagy in MPP+-induced Parkinson's disease model

Authors: *F. JIAO, X. LI, X. WANG, Y. WU;
Shandong Key Lab. of Behavioral Med., Sch. of Mental Health, Jining Med. Univ., Jining, China

Abstract: Parkinson's disease is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons. Dysregulation of the autophagy pathway has been observed in Parkinson's disease, but the underlying molecular mechanism remains poorly understood. The transcription factor EB (TFEB) was recently shown to regulate multiple genes in the autophagy process. Here we have identified that Cdk5, a serine/threonine kinase that is abnormally activated in Parkinson's disease, directly phosphorylates TFEB at Ser109 and represses TFEB nuclear translocation. This phosphorylation inhibits the expression of autophagy genes, leading to dysregulation of the autophagy pathway. Interruption of Cdk5-TFEB pathway increases TFEB transport to the nucleus, mediates the expression of autophagy genes and attenuates MPP^+-induced neuronal cells death. Thus, activation of Cdk5 may be served as a critical signal to regulate the autophagy pathway by modulating TFEB nuclear translocation in Parkinson's disease.

Disclosures: F. Jiao: None. **X. Li:** None. **X. Wang:** None. **Y. Wu:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.12

Topic: C.03. Parkinson's Disease

Support: DOD Grant W81XWH-12-1-0039
DOD Grant W81XWH-10-1-0640
JPB Foundation, Award #475

Title: Loss of SATB1 induces a p21 dependent cellular senescence phenotype in dopaminergic neurons

Authors: *M. RIESSLAND[1], B. KOLISNYK[1], T. KIM[2], J. CHENG[1], J. NI[1], J. A. PEARSON[1], E. J. PARK[1], K. DAM[1], D. ACEHAN[1], L. S. RAMOS-ESPIRITU[1], W. WANG[1], J. ZHANG[1], J.-W. SHIM[3], G. CICERI[2], L. BRICHTA[1], L. STUDER[2], P. GREENGARD[1];
[1]Rockefeller Univ., New York, NY; [2]Ctr. for Stem Cell Biol., Mem. Sloan-Kettering Cancer Ctr., New York, NY; [3]Soonchunhyang Inst. of Medi-bio Sci., Cheonan-si, Korea, Republic of

Abstract: Cellular senescence is a mechanism used by mitotic cells to prevent uncontrolled cell division. As senescent cells persist in tissues, they cause local inflammation and are harmful to surrounding cells, contributing to aging. Generally, neurodegenerative diseases, such as Parkinson's, are disorders of aging. The contribution of cellular senescence to neurodegeneration is still unclear. SATB1 is a DNA binding protein associated with Parkinson's disease. We report that SATB1 prevents cellular senescence in post-mitotic dopaminergic neurons. Loss of SATB1 causes activation of a cellular senescence transcriptional program in dopamine neurons, both in

human stem cell-derived dopaminergic neurons and in mice. We observed phenotypes which are central to cellular senescence in SATB1 knockout dopamine neurons in vitro and in vivo. Moreover, we found that SATB1 directly represses expression of the pro-senescence factor, p21, in dopaminergic neurons. Our data implicate senescence of dopamine neurons as a contributing factor to the pathology of Parkinson's disease.

Disclosures: **M. Riessland:** None. **B. Kolisnyk:** None. **T. Kim:** None. **J. Cheng:** None. **J. Ni:** None. **J.A. Pearson:** None. **E.J. Park:** None. **K. Dam:** None. **D. Acehan:** None. **L.S. Ramos-Espiritu:** None. **W. Wang:** None. **J. Zhang:** None. **J. Shim:** None. **G. Ciceri:** None. **L. Brichta:** None. **L. Studer:** None. **P. Greengard:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.13

Topic: C.03. Parkinson's Disease

Support: NIH NS093569

Title: Lysosomal and glucocerebrosidase dysfunction promotes the spread of pathology in Parkinson's disease

Authors: ***H. YU**[1], K. CHUNG[2], U. HENGST[2], A. LI[3];
[1]Columbia Univ., New York, NY; [2]Columbia Univ., New York, NY; [3]Mt Sinai Sch. of Med., New York, NY

Abstract: Mutations in the glucocerebrosidase (GC) gene (*gba*) are associated with the most frequent lysosomal storage disorder - Gaucher's disease (GD) - and the most common genetic risk factor for Parkinson's disease (PD) and Dementia with Lewy bodies (DLB). Our understanding of how *gba* mutations result in poor protein and lipid control and promote proteo/lipopathy is an important biological phenomenon in need of investigation on how it is related to earlier disease onset, accelerated progression and cognitive impairment. In this study, we examined the impact of *gba* mutations on the autophagic-lysosomal system and how it results in the spread of pathology through extracellular vesicles and the propagation of pathology from neuron to neuron. We examine the impact of both synuclein- and tau-opathy using dopaminergic neurons from iPSC cells of donors with N370S mutations and age-matched controls and other neuronal models. We compared N370S *gba* dopaminergic neurons with their CRISPR/Cas9 control isogenic control variants, as well as non-PD/mutation dopaminergic neurons that were genetically modified to express the N370S *gba* mutation and found that proteostasis was impaired in the N370S neurons compared to isogenic controls. Further, while we noted increased proteinopathy in N370S neurons, we identified significantly magnified levels of extracellular

vesicles (EVs; largely exosomes and ectosomes) that carried pathological cargo, including S-129 α-synuclein, phospho-tau and the aggresome protein, p62. We also noted that EV lipids and proteins contained higher proportions of autophagic-late endosomal-lysosomal origin indicating it may be a mechanism for intracellular control when the lysosomal system is failing. To identify if EVs from *gba* mutation carriers were proteotoxic and could spread pathology, we used a microfluidic system, a useful model for pathological spread, to test if EVs isolated from brains of *gba* mutant carriers were more likely to promote proteinopathy from one neuronal population to the next than when compared to EVs from non-demented controls in non-GC disrupted neurons. Our work successfully supported the hypothesis that EVs from *gba* carriers with DLB produced more pathology in neuron population and that this could transmit to an adjoining neuronal population isolated in the microfluidic system, representing a mechanism for how *gba*-PD/DLB develops and pathologically progresses.

Disclosures: H. Yu: None. **K. Chung:** None. **U. Hengst:** None. **A. Li:** None.

Nanosymposium

629. Parkinson's Disease: Cellular Mechanisms

Location: Room N426

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 629.14

Topic: C.03. Parkinson’s Disease

Support: NIH NINDS R01NS092823

Title: Gba1 dysfunction in novel isogenic Parkinson's disease iPSC models that harbor the SNCA triplication mutation

Authors: *I. STOJKOVSKA, F. ZUNKE, N. R. BELUR, J. R. MAZZULLI;
Northwestern Univ., Chicago, IL

Abstract: Parkinson's disease (PD) is pathologically characterized by the accumulation of protein inclusions whose major component is alpha-synuclein (a-syn). Multiplications of *SNCA*, which encodes for a-syn, lead to autosomal dominant PD with dementia in which the clinical severity is dependent on a-syn gene dosage. However, the molecular mechanism by which the natural overexpression of a-syn contributes to PD pathogenesis is unknown. To examine the mechanisms of a-syn toxicity, we developed and characterized novel induced pluripotent stem cell (iPSC)-derived midbrain models from three individual PD patients that carry a triplication in the *SNCA* gene locus. PD-derived midbrain cultures exhibit many features of the PD brain such as accumulation of insoluble a-syn and the presence of amyloidogenic a-syn inclusions. Using a combination of biochemical and ultrastructural analyses, we show that subsequent to inclusion formation, PD-derived culture models exhibit defects in protein trafficking, including accumulation of immature forms of the lysosomal enzyme β-glucocerebrosidase (GCase), and

reduced lysosomal function. Using the double-nicking CRISPR/Cas9 system to reduce a-syn, we also generated and characterized isogenic PD-iPSC lines, which demonstrate an improvement in GCase protein trafficking and lysosomal function. Our findings suggest that a-syn accumulation leads to protein trafficking and lysosomal dysfunction of GCase. Strategies that enhance GCase trafficking and lysosomal activity may reduce a-syn and provide benefit to patients with PD and related synucleinopathies.

Disclosures: I. Stojkovska: None. **F. Zunke:** None. **N.R. Belur:** None. **J.R. Mazzulli:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lysosomal Therapeutics Inc.

Nanosymposium

630. LRRK2 Function in Health and Disease

Location: Room S401

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 630.01

Topic: C.03. Parkinson's Disease

Support: NIH (R01 NS091719)
Van Andel Research Institute

Title: Contribution of the Roc-COR tandem domain to dimerization and activity of LRRK2

Authors: *L. A. WYMAN[1,2], D. J. MOORE[2];
[1]Van Andel Inst. Grad. Sch., Grand Rapids, MI; [2]Ctr. for Neurodegenerative Sci., Van Andel Inst., Grand Rapids, MI

Abstract: Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene are the most frequent cause of late-onset, autosomal dominant familial Parkinson's disease (PD). LRRK2 is a member of the ROCO protein superfamily, characterized by multiple domains including a conserved Ras-of-Complex (Roc) GTPase and a kinase domain separated by the C-terminal-of-Roc (COR) domain. Although the mechanism is unclear, an intact Roc GTPase domain is critically required for kinase activity and is important for LRRK2-mediated neuronal toxicity. LRRK2 is proposed to function via a G protein activated by dimerization (GAD) mechanism where dimerization regulates the GTPase cycle, however it remains unclear which domains and residues of LRRK2 are important for dimerization. Based on findings from our lab and others, we *hypothesize* that LRRK2 dimerization is predominantly mediated by the Roc-COR tandem domain. Disrupting critical interactions within the dimerization interface could potentially serve as a useful strategy to impair LRRK2 enzymatic activity and therefore to attenuate mutant LRRK2-mediated neurotoxicity. We have initially mapped interactions between the isolated Roc and COR domains of LRRK2 supporting the capacity for robust COR:COR and Roc:COR interactions. Accordingly, we have generated several hypothesis-testing missense mutations within predicted

dimerization or intramolecular interaction interfaces of the Roc-COR tandem domain based upon homology with related prokaryotic ROCO proteins. Intriguingly, we demonstrate that combining disrupting mutations in the Roc (H1405P) and COR (N1577P) domains of LRRK2 reduces its binding affinity to form hetero-dimers with wild-type LRRK2 and alters the molecular mass of native LRRK2 complexes, supporting an impaired capacity for dimerization. Consistent with this effect, the H1405P/N1577P LRRK2 variant exhibits reduced cellular phosphorylation of LRRK2 at Ser1292 and the kinase substrate RAB10, as well as impaired GTP-binding activity. We are now attempting to correlate the dimerization capacity of LRRK2 with its subcellular localization and ability to induce neuronal toxicity. We aim to demonstrate as a proof-of-concept whether disrupting LRRK2 dimerization can provide a neuroprotective strategy for *LRRK2*-mediated neurodegeneration in PD.

Disclosures: L.A. Wyman: None. **D.J. Moore:** None.

Nanosymposium

630. LRRK2 Function in Health and Disease

Location: Room S401

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 630.02

Topic: C.03. Parkinson's Disease

Support: Intramural Research Grants
MJFF

Title: The scaffold domains of the Parkinson's disease protein leucine-rich repeat kinase 2 (LRRK2) are key in the regulation of its autophagic function

Authors: *S. COGO[1], C. MANZONI[2], D. TRABZUNI[3], L. CIVIERO[1], L. BUBACCO[1], E. KEVEI[2], P. LEWIS[2], E. GREGGIO[1];
[1]Univ. of Padova, Padova, Italy; [2]Univ. of Reading, Reading, United Kingdom; [3]UCL Queen Square Inst. of Neurol., London, United Kingdom

Abstract: Mutations in *Leucine-rich repeat kinase 2* (*LRRK2*) represent the single most prevalent genetic cause of familial Parkinson's disease (PD) and common variants act as risk factors in sporadic PD. LRRK2 is characterized by the presence of dual enzymatic activities, i.e. GTPase and a serine-threonine kinase, cross-talking to each other and with the surrounding scaffold regions. The majority of PD mutations sit in the catalytic core and increase kinase activity, leading to cellular toxicity. Hence, over the past 15 years LRRK2 kinase activity has been addressed as a promising therapeutic target. However, our current understanding of the intramolecular mechanisms of regulation and the physiopathology of LRRK2 is still incomplete. Recent findings suggest an involvement of LRRK2 in the regulation of autophagy and the endo-lysosomal pathway, with evidence mainly coming from knockout (KO) models or after

inhibition of kinase activity, which is capable to induce autophagy. Here, we aim to dissect the contributions of kinase, GTPase and scaffold moieties on the physiology of LRRK2, taking advantage of murine RAW264.7 macrophages expressing endogenous levels of GTP-binding deficient T1348N-Lrrk2 and *C. elegans* expressing the ortholog of the GTP-free K1347A variant knocked-in at the endogenous LRK1 locus (K988A). Nucleotide-free Lrrk2 is depleted of both catalytic activities but maintains the scaffold shell. Our data indicate a significant impact of the T1348N mutation on Lrrk2 steady state levels, both at mRNA and protein level, which do not correlate with a differential stability or turnover as compared to the wild-type (WT). When evaluating basal autophagic markers, we observed an accumulation of p62 - an autophagic cargo and a recently described LRRK2 kinase substrate - in the T1348N cell line, which is absent in KO cells. This correlates with an aberrant accumulation of endo-lysosomal and autophagic vesicles, along with multilamellar bodies, in the mutant line as compared to the WT, as highlighted by electron microscopy analysis, possibly suggestive of an impairment in autophagy-dependent degradative pathways. In addition, T1348N-Lrrk2 cells displayed alterations in the ability to respond to autophagy induction via mTOR and to promote autophagosome formation after stress treatments (e.g. chloroquine, MG132). Our data so far suggest that the scaffold regions of Lrrk2 likely mediate key autophagic events, but the catalytic hub is required to guarantee a proper equilibrium in the degradative flux.

Disclosures: S. Cogo: None. **C. Manzoni:** None. **D. Trabzuni:** None. **L. Civiero:** None. **L. Bubacco:** None. **E. Kevei:** None. **P. Lewis:** None. **E. Greggio:** None.

Nanosymposium

630. LRRK2 Function in Health and Disease

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Topic: C.03. Parkinson’s Disease

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American Parkinson Disease Association (APDA) Research Grant
NIH/NIGMS P20 GM113109
KSUCVM SUCCESS-FYI Intramural Grant

Title: LRRK2 regulates AP2 phosphorylation cycles to mediate endocytosis

Authors: Q. LIU, J. YU, *Y. XIONG;
Dept. of Anat. and Physiol., Kansas State Univ., Manhattan, KS

Abstract: Recent compelling genetic evidence revealed that endocytic membrane-trafficking pathway plays a major role in the risk of Parkinson’s disease (PD). The most commonly mutated LRRK2 protein in PD has been demonstrated to cause defects in cellular trafficking including

endocytosis. However, how LRRK2 mediates endocytosis is largely unknown. Endocytosis is a complex biological process involving many regulatory mechanisms. Among these, the AP2 complex, recently implicated to be relevant for PD risk, is a core component in clathrin-mediated endocytosis (CME). The function of AP2 is tightly regulated by its dynamic phosphorylation status. Phosphorylation of AP2 is required for its membrane association and initial clathrin coated vesicle (CCV) formation. After CCV scission, AP2 dephosphorylation promotes its uncoating from CCVs, a critical process required for the new cycle of CCV formation. Here we identified LRRK2 as a kinase for AP2 to regulate AP2 phosphorylation cycles and its function in CME. Our study showed that abnormal AP2 phosphorylation cycles, either by knockout or overexpression of LRRK2, cause endocytotic defects. Further, we found that phosphorylation of AP2 by LRRK2 mediates LRRK2-induced neuronal toxicity both *in vitro* and *in vivo* in *Drosophila* dopamine neurons. Taken together, our study provides a direct mechanistic link between LRRK2 and endocytosis in PD pathogenesis.

Disclosures: Q. Liu: None. **J. Yu:** None. **Y. Xiong:** None.

Nanosymposium

630. LRRK2 Function in Health and Disease

Location: Room S401

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Presentation Number: 630.04

Topic: C.03. Parkinson's Disease

Support: MJFF
NIH 1RF1AG057247
T32 NS 96050-21

Title: LRRK2: Lurking between the brain and gut

Authors: *M. HERRICK, M. HOUSER, C. KEATING, L. SNIFFEN, J. CHANG, M. G. TANSEY;
Emory Univ., Atlanta, GA

Abstract: <u>Importance:</u> Links between Parkinson's disease (PD) and the gastrointestinal system have become increasingly common. Mutations in Leucine Rich Repeat Kinase 2 (LRRK2) are known as the greatest genetic contributor to PD and associated with sporadic PD and increased risk for Crohn's disease (CD). G2019S, the most common LRRK2 inherited PD mutation, results in an increased toxic gain-of-function kinase activity. Similarly, the newly identified LRRK2 N2081D SNP results in a gain-of-function increase in kinase activity; and it is associated with a two-fold higher risk for CD, highlighting the need to further understand LRRK2's role in PD and CD. **<u>Objective:</u>** Given the role of LRRK2 in PD and CD, we sought to directly investigate the role of increased LRRK2 protein and increased gain-of-function kinase activity on the gut-brain

axis. **Methods:** BAC transgenic mice overexpressing mouse wildtype or G2019S LRRK2 were subjected to acute DSS-induced colitis and monitored daily for weight loss and disease activity indexes. **Results:** Data suggests G2019S mice are more susceptible to acute DSS-induced colitis. Due to this intestinal insult, G2019S mice exhibited: increased colonic inflammation, altered colonic tight junction proteins, a reduction in CD4 T cell PBMC populations, increased CD8 T cell infiltration to the brain and increased microglia antigen presentation. **Conclusions:** G2019S mice are more susceptible to intestinal inflammation thereby resulting in increased neuroinflammation and neuropathology. Given that anti-tumor necrosis factor (TNF) therapy reduces the risk of PD in patients with irritable bowel disease, ongoing studies are determining if soluble TNF (sTNF) inhibition rescues G2019S phenotypes. Completion of these studies will advance our understanding of alterations in LRRK2 levels and activity to the gut-brain axis and may reveal therapeutic opportunities for the use of sTNF inhibitors to delay or mitigate peripheral (gut) inflammation to lower the risk of brain inflammation and age-related neurodegeneration.

Disclosures: M. Herrick: None. **M. Houser:** None. **C. Keating:** None. **L. Sniffen:** None. **J. Chang:** None. **M.G. Tansey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent. Xencor.

Nanosymposium

630. LRRK2 Function in Health and Disease

Location: Room S401

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 630.05

Topic: C.03. Parkinson's Disease

Support: MJFF15882

Title: Discovery of novel kinase-activating LRRK2 mutations in emerging genome-wide sequencing datasets

Authors: *N. BRYANT-GARNER[1], A. B. WEST[2];
[1]Pharmacol. & Cancer Bio, [2]Ctr. for Neurodegeneration and Neurotherapeutics, Duke Univ., Durham, NC

Abstract: Mutations in the Leucine Rich Repeat Kinase 2 (*LRRK2*) gene can cause Parkinson's Disease (PD) and are some of the most common genetic causes of neurodegeneration. The *LRRK2* gene encodes a multi-domain protein and emerging genome sequencing efforts in PD cases are revealing dozens of extremely rare mutations in conserved residues in core enzymatic domains. Using sequencing data from the Parkinson's disease Progression Markers Initiative (PPMI), collectively, the rare variants in conserved residues could significantly add, perhaps double, the number of PD cases caused by LRRK2 mutations, if the rare variants are proven

pathogenic. Herein we profile the functional effects of rare LRRK2 variants picked from ongoing genome-sequencing efforts with respect to LRRK2 autophosphorylation, trans-Rab phosphorylation, and localization to endosomes and Golgi. LRRK2 kinase activation is the molecular consequence of known pathogenic mutations, however, the downstream mechanisms underlying this effect remains unclear. We speculate that enhanced LRRK2-recruitment to recycling endosomes and the trans-Golgi-network may underlie some aspects of the functional effects of LRRK2 pathogenic mutations. With LRRK2 targeted therapies in development it is imperative to characterize downstream mechanisms of kinase activation. Identifying which protein partners are at play in disease relevant contexts provides much needed information on PD pathomechanisms, cellular implications of LRRK2 inhibitors and even additional intervention targets.

Disclosures: **N. Bryant-Garner:** None. **A.B. West:** None.

Nanosymposium

630. LRRK2 Function in Health and Disease

Location: Room S401

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Presentation Number: 630.06

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation
JPB Foundation

Title: Regulation of levodopa-induced dyskinesia by leucine-rich repeat kinase 2 in a mouse model of Parkinson's disease

Authors: *R. MARONGIU, L. VELAZQUEZ, J. L. JOYCE, M. G. KAPLITT;
Weill Cornell Med., New York, NY

Abstract: The gold standard for Parkinson's disease (PD) treatment is the administration of the dopamine precursor L-dopa. However, ~80% of patients develop motor complications called abnormal involuntary movements (AIMs) or L-dopa-induced dyskinesia (LID), which constitutes a major cause of disability and limit therapeutic efficacy. When nigral dopaminergic neurons degenerate, L-dopa treatment can cause LID by altering medium spiny neuron function in the dorsal striatum. Recent data suggest that LRRK2 is associated with several key regulators of LID and may be important for striatal response to PD dopaminergic therapy. We hypothesize that disruption of LRRK2 levels via either PD-associated G2019S mutation or inhibition of endogenous LRRK2 with short-hairpin RNA (shRNA) interference promotes LID in the unilateral 6-hydroxydopamine (6OHDA) mouse model of PD. To test the influence of endogenous LRRK2 on LID, we injected an AAV vector to inhibit mouse LRRK2 (AAV.sh.LRRK2), or control vector (AAV.sh.Luciferase), into the dorsal striatum ipsilateral to

the 6OHDA lesion in C57Bl/6 mice. Upon quantifying the lesion efficiency via apomorphine-induced rotations (0.25 mg/kg), we induced LID by daily administration of L-dopa (weekly escalating doses of 3, 6, or 12 mg/kg) and scored locomotor, axial, limb and orolingual AIMs for 3 weeks. We observed that inhibition of striatal LRRK2 levels significantly increases LID scores by 40% compared to control mice, suggesting that striatal LRRK2 may be a key regulator of the LID response to dopaminergic therapy. To evaluate the role of mutations affecting LRRK2 activity on LID, we 6OHDA lesioned knock-in (KI) mice homozygous for the G2019S mutation, known to increase LRRK2 kinase activity, and wild type (wt) littermates. Upon induction of LID as reported above, we surprisingly found that G2019S mutation significantly reduces limb-orolingual AIMs, whereas increasing locomotor rotational behavior.Altogether, our data demonstrate that optimal levels and activity of LRRK2 are necessary for proper response of the dorsal striatum to dopaminergic treatment in PD mice. These also raise questions about the potential unintended effects of experimental treatments targeting LRKK2 inhibition on the response to dopaminergic therapy in PD patients. Therefore, to test if inhibition of LRRK2 activity may influence response to L-dopa, we treated our dyskinetic G2019S KI and wt mice with the LRRK2 kinase inhibitor MLi-2 during one AIM session. We found no significant effect of MLi-2 on all the AIMs. However, this does not preclude the possibility that chronic LRRK2 inhibitors treatment in combination with L-dopa could lead to different outcomes.

Disclosures: R. Marongiu: None. **L. Velazquez:** None. **J.L. Joyce:** None. **M.G. Kaplitt:** None.

Nanosymposium

630. LRRK2 Function in Health and Disease

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Presentation Number: 630.07

Topic: C.03. Parkinson’s Disease

Support: R01NS093383 to WWS
R21NS096620 to WWS

Title: LRRK2 GTP-binding inhibitors increase Lewy body-like inclusions

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Abstract: Parkinson’s disease (PD) is one of most common movement disorders with loss of dopaminergic neurons and presence of Lewy bodies in certain brain areas. Mutations in Leucine-rich repeat kinase 2 (LRRK2) can cause genetic form of Parkinson’s disease (PD) and contribute

to sporadic PD. LRRK2 contains both kinase and GTPase activities that have implications in PD pathogenesis. We recently have identified several LRRK2 GTP binding inhibitors that reduces LRRK2-linked neurodegeneration. Here we found that pharmacological inhibition of GTP-binding by GTP binding inhibitors (68 and Fx2149) increased LRRK2-linked ubiquitination predominantly via K27 linkage. Compound 68- or Fx2149 increased G2019S-LRRK2-linked ubiquitinated aggregates occurred through the atypical linkage types K27, and K63. Co-expression of K27R and K63R, that blocked the ubiquitination via K27 and K63 linkage, reversed the effects of 68 and Fx2149. Moreover, 68 and Fx2149 also promoted G2019S-LRRK2-linked aggresome (Lewy body-like inclusion) formation via K27 and K63 linkage. These findings demonstrate that LRRK2 GTP-binding activity is critical in LRRK2-linked ubiquitination and aggregation formation. Inhibition of LRRK2 GTP binding activity may lead the cells undergoing a self-protection mechanism by sequestering the toxic mutant proteins into inclusions.

Disclosures: X. Wang: None. **J.M. Thomas:** None. **G. Guo:** None. **F.C. Nucifora Jr:** None. **L.G. Nucifora:** None. **X. Sun:** None. **F. Xue:** None. **C.A. Ross:** None. **W. Smith:** None.

Nanosymposium

631. Cellular Mechanisms of Tauopathies

Location: Room S103

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 631.01

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: NIH R21AG058080

Title: Internalized prion-like tau seeds are aberrantly processed resulting in a distinct post-translational signatures

Authors: *J.-H. TSENG, T. J. COHEN;
Neurol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: The prion-like spread of tau pathology could underlie a spectrum of distinct clinical tauopathies including Alzheimer's disease (AD). Although evidence indicates that tau seeds are transmissible, it is unclear how they are internally processed. Here, we analyzed wild-type and disease-associated P301L tau seeds using in vitro and neuron-based assays. Unexpectedly, we show that P301L seeds are aberrantly modified within the microtubule-binding repeat domain (MTBR) via acetylation and phosphorylation in not only neurons but other cell types in the brain. While these modifications do not alter tau seed trafficking, processing, or localization, acetylation at specific residues significantly accelerated tau aggregation kinetics, primed tau pathological modifications at nearby residues, and enhanced tau templating propensity. We demonstrate that tau seeds directly associate with deacetylases, providing a mechanism to

explain the susceptibility of internalized seeds to lysine acetylation. Furthermore, we provide evidence that tau seeds require endogenous tau for full pathogenicity. Our study reveals complex post-translational changes that could underlie tau strain identity and also hints as poorly characterized roles for tau other than as a microtubule stabilizer. Our findings may provide valuable insights into the biological properties of propagated tau species as well as the potential roles of tau as a regulator of cytoplasmic signaling pathways in AD and related tauopathies.

Disclosures: J. Tseng: None. **T.J. Cohen:** None.

Nanosymposium

631. Cellular Mechanisms of Tauopathies

Location: Room S103

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 631.02

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: DZNE
MPG
Cure Alzheimer Fund

Title: Adenosine A1 receptor antagonist rolofylline reverses synaptopathy in a mouse model of Tau pathology

Authors: T. SAMADDAR[1], E.-M. MANDELKOW[1,2];
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Abstract: Aggregation of the neuronal protein Tau has been established as a hallmark of several neurodegenerative diseases; however, the precise mode of action of toxic Tau is poorly understood. Previous work in our lab, using a mouse model expressing a proaggregant mutant form of full-length human Tau (TauΔK280), had shown that the animals have reduced neuronal activity (paired-pulse ratio, basal synaptic transmission) and spatial memory deficits. However, treatment with the adenosine A1 receptor antagonist rolofylline (KW-3902) was able to reverse the synaptic deficits in the hippocampus and to restore spatial memory in these mice [Dennissen et al., PNAS 2016]. Here, we investigate the molecular mechanism by which rolofylline improves the neuronal functions in the TauΔK280 mice. Biochemical characterization of the presynaptic terminals in the hippocampal neurons revealed a reduction of the total pool of synaptic vesicles in TauΔK280 mice compared to its littermate controls. The cAMP-dependent activation of protein kinase A (PKA), a signaling pathway known to influence presynaptic vesicle release, was also reduced in TauΔK280 mice (reduced phosphorylated substrates of PKA and reduced CREB phosphorylation). Postsynaptic biochemical fractions from TauΔK280 mice showed a reduction of mature dendritic spine markers (PSD-95 and phospho-GluA1). Treatment

with Rolofylline rescued the levels of the total pool of synaptic vesicles and PKA activity in the presynaptic compartment. In the postsynaptic biochemical fraction, rolofylline treatment also restored the levels of mature dendritic spine markers (PSD-95 and phospho-GLuA1) in TauΔK280 mice to littermate control levels. Thus, Rolofylline was able to reverse the suppression of neuronal activity inflicted by pro-aggregant Tau, by boosting the presynaptic vesicle release machinery, as well as increasing the components of postsynaptic glutamatergic synapses in the hippocampal neurons in this mouse model of neurodegeneration. The data are consistent with a scheme whereby proaggregant Tau causes an increase in extracellular adenosine, hence activation of adenosine A1 receptors and decrease of cellular metabolism via G-protein dependent signaling. Blocking A1 receptors liberates the brake and thus reverses the Tau-induced effects.

Disclosures: **T. Samaddar:** A. Employment/Salary (full or part-time):; DZNE (Deutsches Zentrum für Neurodegenerative Erkrankungen), Bonn, Germany. **E. Mandelkow:** A. Employment/Salary (full or part-time):; DZNE (Deutsches Zentrum für Neurodegenerative Erkrankungen), Bonn, CAESAR (Center of Advanced European Studies and Research), Bonn, Germany.

Nanosymposium

631. Cellular Mechanisms of Tauopathies

Location: Room S103

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 631.03

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: GNT1143978
GNT1143848
GNT1136241
GNT1081916
GNT1132524

Title: Proteomics and computational modelling reveals master sites in tau hyperphosphorylation involved in Alzheimer's disease

Authors: *K. STEFANOSKA[1], M. GAJWANI[1], T. MUELLER[1], J. BERTZ[1], G. R. WHITE[2], A. POLJAK[3], L. ITTNER[1], A. ITTNER[1];
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Abstract: Alzheimer’s disease is the most prevalent form of dementia and is characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs).

Hyperphosphorylated tau is the main constituent of NFTs. Despite extensive research, the molecular process that leads to hyperphosphorylated tau is still unclear. Tau is a substrate for several protein kinases that target tau on multiple phosphorylation sites. However, phosphorylation at one site may impact on activity of kinases at different sites on tau. As a result, tau phosphorylation events may follow an intrinsic hierarchy. Here, we address this concept focusing on proline-directed tau phosphorylation. We used experimental data from 21-proline-directed sites and 15-proline-directed kinases as the foundation for computational modelling of multi-site tau phosphorylation. We show that tau phosphorylation at different sites is modulated by a complex interdependence hierarchy. For the first time, we identify 'Master' phosphorylation sites at the center of this hierarchy, which are essential in shaping modification at other sites, thus determining the propagation of tau hyperphosphorylation. Furthermore, we have identified the kinases that have the strongest impact at 'Master' sites, providing a complex network of phosphorylation events. Our interdisciplinary approach thus delineates a hierarchy in tau phosphorylation with implications for tau hyperphosphorylation and NFT formation. Our results may inform future therapeutic intervention to target specific sub-species of tau.

Disclosures: **K. Stefanoska:** None. **M. Gajwani:** None. **T. Mueller:** None. **J. Bertz:** None. **G.R. White:** None. **A. Poljak:** None. **L. Ittner:** None. **A. Ittner:** None.

Nanosymposium

631. Cellular Mechanisms of Tauopathies

Location: Room S103

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 631.04

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Title: Onset of neuronal network aberrations and memory deficts in P301S tau transgenic mice is linked to a signature of immediate early genes

Authors: M. PRZYBYLA[1], J. VAN EERSEL[1], J. VAN DER HOVEN[1], A. VAN HUMMEL[1], C. STEVENS[2], A. HARASTA[1], J. MULLER[3], Y. KE[1], J. POWER[4], G. HOUSLEY[4], T. KARL[5], M. KASSIOU[6], A. ITTNER[1], L. ITTNER[1];
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Abstract: Hyperphosphorylation and deposition of tau in the brain is a characteristic feature of neurodegenerative diseases, including frontotemporal dementia (FTD) and Alzheimer's disease

(AD). Furthermore, tau - but not Aβ pathology - correlates with cognitive decline and neurodegeneration in these diseases. However, very little is known about how tau pathology drives cellular and molecular mechanisms in cognitive decline. Therefore, this study aims to characterize the effects of transgenic P301S mutant human tau expression on neuronal network function in the murine hippocampus utilizing the TAU58/2 tau transgenic mouse model. These mice express human P301S mutant tau and recapitulate essential features of AD and FTD, including tau pathology, early onset disinhibition and moderate motor deficits. Here, we found that the onset of progressive spatial memory decline in TAU58/2 transgenic mice was accompanied by deficits in long-term potentiation (LTP) and neuronal network aberrations during electrophysiological and electroencephalography (EEG) recordings. Further, gene-expression profiling at onset of deficits in TAU58/2 mice indicated an immediate early genes (IEG) signature that is consistent with neuronal network hypersynchronicity. Finally, we determined that increased IEG activity limited to neurons harbouring tau pathology, providing a direct link between abnormal tau and network dysfunction. Taken together, our data suggests that tau pathology drives neuronal network dysfunction by hyperexcitation of individual, pathology-harbouring neurons and is a major contributor to memory deficits. This study provides new insights into the pathomechanistic role of tau in disease and may thereby allow the identification of new targets for future translations into therapy.

Disclosures: **M. Przybyla:** None. **J. van Eersel:** None. **J. van der Hoven:** None. **A. van Hummel:** None. **C. Stevens:** None. **A. Harasta:** None. **J. Muller:** None. **Y. Ke:** None. **J. Power:** None. **G. Housley:** None. **T. Karl:** None. **M. Kassiou:** None. **A. Ittner:** None. **L. Ittner:** None.

Nanosymposium

631. Cellular Mechanisms of Tauopathies

Location: Room S103

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 631.05

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: R01 NS073899
R01 MH103848

Title: Ppiases have divergent effects on tau aggregation and toxicity

Authors: J. D. BAKER, S. RODRIGUEZ OSPINA, ***L. J. BLAIR**;
Univ. of South Florida, Tampa, FL

Abstract: Accumulation of neurotoxic tau is a hallmark of Alzheimer’s disease and related tauopathies. We and others have demonstrated that molecular chaperones have a major impact on this process. Recently, we discovered that Cyclophilin 40 (CyP40), a molecular chaperone with

peptidyl prolyl-isomerase (PPIase) activity, can break up tau aggregates. Now, we have begun to investigate additional cyclophilin family members. Interestingly, we have found similar disaggrease activity in PPIE a closely related cyclophilin. However, experiments using recombinant proteins, tau cells models and AAV overexpression in tau transgenic mice revealed that, unlike CyP40, PPIE-mediated untangling was only temporary and actually seeded additional tau aggregation. Work is ongoing to better characterize this interaction and understand the differences between CyP40 and PPIE on tau that lead to such discrepant effects. These data highlight the unique activity of CyP40 to beneficially break apart tau aggregates.

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Nanosymposium

631. Cellular Mechanisms of Tauopathies

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NIH/NIA 1R01AG059639

Title: The role of tau interactome in the neurotoxicity and propagation of tau oligomers in neurodegenerative tauopathies

Authors: Y. YOU[1], S. XIANG[1], A. PERKINS[1], Y. YOU[1], E. ALLMAN[1], P. CISTERNAS[1], A. OBLAK[1], J. C. TRONCOSO[2], J. ZHANG[1], ***C. A. LASAGNA-REEVES**[1];
[1]Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Neuropathol Lab., Johns Hopkins University, Sch. of Med., Baltimore, MD

Abstract: Pathological aggregation of the microtubule-associated protein tau and the preponderance of neurofibrillary tangles (NFT) or other inclusions containing tau are defining histopathological features of Alzheimer's disease (AD) and many neurodegenerative diseases collectively known as tauopathies including Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal lobar degeneration (FTLD). During the past decade, a major focus of research has been the understanding of the propagation of pathological tau in AD patient brains that follow neuronal networks. Despite the knowledge acquired, until now, the cellular mechanism involved in tau propagation, the nature of the tau species involved in the spreading, and the precise seeding/template remains unclear. To identify the tau species responsible for propagation, we performed size exclusion chromatography (SEC)

of brain samples from tau-transgenic mice as well as from brain extracts from AD and PSP patients, followed by a cell-based seeding assay. We established how tau forms *in vivo* a high molecular weight oligomeric-complex with a strong seeding activity. We then performed tau-immunoprecipitation followed by Mass Spectrometry analysis. Mass Spec. results revealed that this tau-pathological-complex interacts with different proteins that do not interact with tau physiological monomers. After performing Ingenuity pathway analysis (IPA) we determined how several pathways associated to synapses are enriched within proteins interacting with this tau-pathological-complex and how many of these interactors are known AD genetic risk factors based on GWAS studies. Interestingly, IPA also revealed that synaptic pathways are enriched within proteins interacting with tau physiological monomers, but in a lower degree. Our findings suggest that a high molecular weight oligomeric-complex is the tau species responsible for propagation, and this tau complex interacts with synaptic proteins that can work as a scaffold to stabilize and facilitate the trans-synaptic spreading of this tau species. Modulating the interaction between tau and synaptic proteins within this pathological-complex responsible for tau propagation could be a therapeutic entry point for AD and other tauopathies.

Disclosures: Y. You: None. **S. Xiang:** None. **A. Perkins:** None. **Y. You:** None. **E. Allman:** None. **P. Cisternas:** None. **A. Oblak:** None. **J.C. Troncoso:** None. **J. Zhang:** None. **C.A. Lasagna-Reeves:** None.

Nanosymposium

631. Cellular Mechanisms of Tauopathies

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Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: NIH R01 NS090934

Title: Single nucleus RNAseq identifies cell type-specific effects of LDLR overexpression or Apoe knockout corresponding with attenuated tau-dependent neurodegeneration

Authors: Y. SHI, P. ANDHEY, I. CHRISTINA, K. YAMADA, K. ZAITSEV, J. LONG, M. MANIS, J. REMOLINA-SERRANO, R. HOYLE, M. ARTYOMOV, ***J. D. ULRICH**, D. M. HOLTZMAN;
Washington Univ. of St Louis, St. Louis, MO

Abstract: Recent studies identified ApoE as playing a critical role in inflammatory glial activation and neurodegeneration. ApoE ablation in P301S tau transgenic mice markedly reduces tau-associated brain atrophy and neuroinflammation, and shifts tau pathology towards an early-disease pattern. Therefore, targeting ApoE levels in the CNS may be an efficient therapeutic approach to ameliorate tau-mediated neurodegeneration. Low-density lipoprotein receptor

(LDLR) is a major apoE receptor that can strongly regulate apoE levels in the CNS via receptor-mediated endocytosis and degradation. By generating P301S mice carrying a PrP-driven LDLR transgene overexpressing murine LDLR by over 10 fold, we found P301S/LDLR mice exhibit significantly reduced brain atrophy and increased brain weight. LDLR overexpression reduced soluble brain ApoE levels by ~90% without altering soluble or insoluble tau levels, but markedly reduced phosphorylated tau (p-tau) levels in salt-soluble and detergent-soluble fractions and shifted p-tau pathology towards early-disease patterns, a phenotype resembling ApoE-deficient P301S mice. Since both LDLR overexpression and global knockout of ApoE resulted in neuroprotective phenotypes, we used single nucleus RNAseq to investigate whether these genetic interventions exhibited shared or dissimilar effects on cell-type specific transcriptomic changes induced by tauopathy. P301S mice exhibited robust gene expression changes in microglia and astrocytes compared to WT mice, consistent with a critical role for glial inflammation in tau-dependent neurodegeneration. Gene set enrichment analysis of microglia and astrocytes found upregulation of interferon and TNFa signaling pathways in P301S mice. We also observed cell-type specific enrichment of lysosomal pathways in microglia and decreased cholesterol biosynthesis in astrocytes from P301S mice. Interestingly, we found that ApoE KO and LDLR overexpression resulted in comparatively stronger reversal of tau-dependent gene expression changes in microglia and astrocytes, respectively. Moreover, despite reductions in several disease-associated microglial markers such as Spp1, Itgax, and Cd74, lysosomal enzyme transcripts in microglia remained elevated in ApoE KO and LDLR overexpressing P301S mice. Overall, our results indicate that reducing apoE levels in the brain via LDLR overexpression is neuroprotective and identify unique pathways in astrocytes and microglia as additional targets for treating tau-dependent neurodegeneration.

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Nanosymposium

631. Cellular Mechanisms of Tauopathies

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Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

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NIH/NINDS U54 NS100717
Tau Consortium Investigator Award
Allen Distinguished Investigator Award

Chan-Zuckerberg Biohub Investigator Award

Title: Elucidating cellular mechanisms of neurodegenerative diseases with CRISPR-based genetic screens in iPSC-derived neurons and glia

Authors: R. TIAN, A. SAMELSON, K. LENG, N. DRÄGER, E. LI, G. MOHL, ***M. KAMPMANN**;
UCSF, San Francisco, CA

Abstract: Human genes associated with brain-related diseases are being discovered at an accelerating pace. A major challenge is the identification of the mechanisms through which these genes act, and of potential therapeutic strategies. To elucidate such mechanisms in human cells, we established a CRISPR-based platform for genetic screening in human iPSC-derived neurons, astrocytes and microglia. Our approach relies on CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa), in which a catalytically dead version of the bacterial Cas9 protein recruits transcriptional repressors or activators, respectively, to endogenous genes to control their expression, as directed by a small guide RNA (sgRNA). Complex libraries of sgRNAs enable us to conduct genome-wide or focused loss-of-function and gain-of-function screens. Such screens uncover molecular players for phenotypes based on survival, stress resistance, fluorescent phenotypes, high-content imaging and single-cell RNA-Seq.
To uncover disease mechanisms and therapeutic targets, we are conducting genetic modifier screens for disease-relevant cellular phenotypes in patient-derived neurons and glia with familial mutations and isogenic controls. In a first pilot application, we have uncovered genes that modulate the formation of disease-associate aggregates of tau in neurons.

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Nanosymposium

631. Cellular Mechanisms of Tauopathies

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Presentation Number: 631.09

Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: SERB-INDIA CRG/2018/004960

Title: Cooperative hydrogen bonding induced amyloid formation: Implications of carbamylation towards neurodegenerative disorders

Authors: *S. GUPTA, J. GADHAVI, P. HIVARE;
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Abstract: Carbamylation is an age-dependent non-enzymatic post-translational modification that typically alters side-chain amine of lysine into uriedo functionality. Though neurodegenerative disorders (NDs) such as Alzheimer's disease or Parkinson's disease are undisputedly correlated with the aging, the connection between carbamylation and NDs has not been explored much. We demonstrate that carbamylation that can potentially cause major structural and functional changes in a given protein owing to extensive hydrogen-bonding network formation also affects the amyloidogenicity of the proteins and peptides implicated in NDs. This effect is very pronounced in short amyloidogenic peptide sequences including those found in tau, α-synuclein, and Aβ. To figure out the origin of this intriguing perturbation, we subjected short polylysine sequences (n=3 to 10) to carbamylation and observed a strong length dependent kinetic amyloidogenic behavior of the resulting polyhomocitrulline sequences. Even for n=3, we could observe a robust amyloid formation which was further substantiated by a range of biophysical characterization including congo-red staining, ANS assay, ThT fluorescence microscopy, AFM and TEM. In silico analysis revealed a strong cooperative inter-sidechain hydrogen bonding induced amyloid formation due to the presence of ureido functionality. In fact, this glue-like hydrogen-bonding offered by homo-citrulline residues so extreme that we could form amyloids from almost any peptide sequence containing dilysine motifs. As amyloid core sequences tau and α-synuclein are lysine-rich, we believe that H-bonding driven amyloid formation initiated by carbamylation events could be the elusive trigger for the onset of amyloid formation.

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Nanosymposium

631. Cellular Mechanisms of Tauopathies

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Topic: C.05. Tauopathies/ Tau-dementias/ and Prion Diseases

Support: R21NS093440
R01NS091329

Title: Pathological tau species coordinate dysregulated ribosomal selectivity: A novel mechanism of dysproteostasis in tauopathies

Authors: S. KOREN[1], M. HAMM[2], H. ZHU[3], S. D'ALTON[2], ***J. F. ABISAMBRA**[2];
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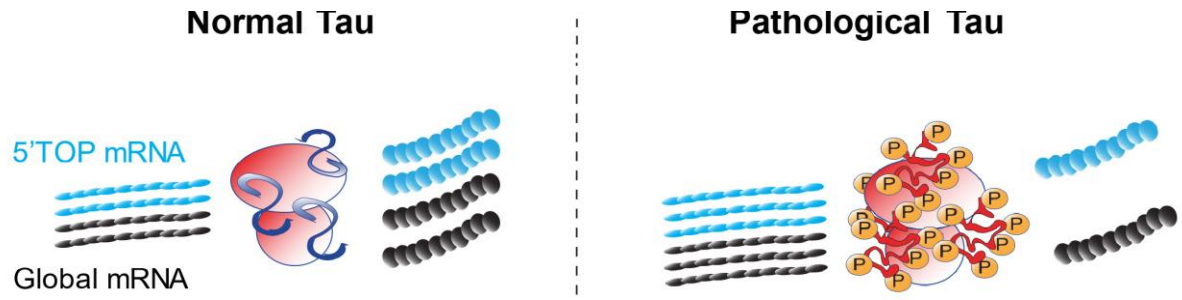
Abstract: Lack of understanding of the molecular mechanisms driving neuronal dysfunction in tauopathies is a major challenge in the field of neurodegenerative disorders. Alterations to the synthesis of new proteins causes major defects in neuronal function, which translates into

cognitive decline that is evident in tauopathies. We recently determined that pathological tau alters RNA translational selectivity in a variety of cell and animal models and also in Alzheimer's disease (AD) brain samples. Remarkably, diminishing tau levels mitigated this effect by reducing tau-ribosome interactions. Moreover, juxtaposing microarray and proteomics, and our development of a novel application to strictly identify the nascent proteome, we establish gene ontologies that are affected by pathological tau in rTg4510 mice where tau levels are expressed or suppressed with doxycycline. Therefore, we identified genes that are critical or non-essential for cognitive rescue in tauopathies. We validated these results in human AD brains and established that translation of 5'TOP mRNAs is specifically diminished in AD brains. We further defined the association of pathological tau species with polysomes in models of tauopathy and AD. We show that reducing tau by inhibiting expression or immunodepletion returns the levels of actively translating ribosomes toward normal and rescues the translation of distinct transcripts associated with actively translating polysomes as determined by RNAseq. Through expression of tau truncations *in vitro* we also identify the regions of tau with the strongest affinity toward binding ribosomes. Together, these data suggest that reducing tau-ribosome interactions rescues selective impairments in protein synthesis and suggest a roadmap for a novel strategy targeting translational dynamics for tauopathies.



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Nanosymposium

632. HIV-Associated Neurocognitive Disorders

Location: Room S403

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 632.01

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant DA034231

Title: HIV-associated cognitive deficits; altered synaptic proteins and spine density correlate with changes in activity-regulated cytoskeleton (Arc) expression

Authors: *Y. K. HAHN[1], S. R. NASS[2], W. D. MARKS[2], A. H. LICHTMAN[2], P. E. KNAPP[1]; [1]Anat. and Neurobio., [2]Pharmacol. and Toxicology, Virginia Commonwealth Universi, Richmond, VA

Abstract: The introduction of combined and highly active anti-retroviral therapies (cART) has transitioned HIV from a disease with short-term survival into a chronic disease, and has changed the profile of HIV-associated neurocognitive disorders (HAND). While severe neurocognitive deficits leading to dementia are now rarely found, the prevalence of mild and moderate cognitive and motor deficits has remained constant or increased, even among patients with systemic viral suppression. This phenomenon likely reflects inefficient penetration of current antiretroviral drugs through the blood brain barrier, which allows the central nervous system (CNS) to exhibit low levels of persistent infection. HIV-infected patients commonly show neurocognitive deficits that affect memory, attention/concentration, mood, and fine motor skills. Furthermore, although the percentage of women in the HIV-infected population has increased, sex-related effects on memory/cognition deficits in HIV patients remain unclear. We utilized a transgenic mouse model of HIV (conditionally expressing HIV-1 Tat_{1-86} protein in CNS) and examined both males and females for changes in cognitive behavior and for expression of biochemical markers related to memory and learning, especially the Arc protein. Arc is an immediate early protein, and its expression can be induced by any environmental experience leading to learning and memory. Altered Arc expression is involved in disruption of memory after radiation therapy. The induction of Arc occurring after contemporaneous acoustic/odor stimuli was reduced by HIV-1 Tat exposure in both sexes, although Arc expression remained significantly higher in Tat^+ females compared to males. Multiple cognitive behavioral tests showed that only Tat^+ males exhibited significant deficits in spatial memory, increased anxiety and altered extinction of fear. Sex-specific differences were also found in both pre- and post-synaptic proteins, and memory-associated proteins like Arc, Homer1, and Zif268 in hippocampal lysates. We also examined spine density in different brain regions; male Tat^+ mice showed significant reductions of spine density in hippocampus and striatum, but not in amygdala. Furthermore, parallel results were seen in levels of Arc protein. Our findings suggest that cognitive deficits of HIV^+ individuals might be influenced by sex-related differences and regional changes in Arc-associated cell signaling.

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Nanosymposium

632. HIV-Associated Neurocognitive Disorders

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH R01 DA018633
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K02 DA027347

Title: Cortico-basal ganglia-thalamo-cortical synaptic circuitry, sociability, and daily life behaviors are affected by HIV-1 Tat and morphine

Authors: *S. R. NASS[1], Y. K. HAHN[2], V. D. MCLANE[1], T. TIAN[1], N. N. ELHAI[2], K. F. HAUSER[1];
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Abstract: Despite the development of antiretroviral therapies, many HIV-1-infected individuals experience deficits in social cognition and emotional processing that interfere with daily living. HIV-1 trans-activator of transcription (HIV-1 Tat) can be expressed in the central nervous system (CNS) and may cause aberrant connectivity within the anterior cingulate cortex (ACC) pathway of the cortico-basal ganglia-thalamo-cortical circuit, underlying these neurocognitive impairments. Additionally, opiates can further exacerbate HIV-1 Tat-induced deficits in function and morphology. Accordingly, we investigated the effects of 8 weeks HIV-1 Tat induction on neuronal synaptic connectivity within the ACC, striatum, and mediodorsal (MD) thalamus, and the effects of HIV-1 Tat and morphine on associated behaviors in adult male transgenic mice. In the ACC, HIV-1 Tat decreased the colocalization of inhibitory pre- and post- synaptic proteins synaptotagmin 2 and gephyrin, respectively, but did not affect the density of layer V pyramidal cell dendritic spines, indicating that in the ACC HIV-1 Tat preferentially interferes with inhibitory synapses. Similarly, HIV-1 Tat did not affect spine density in the MD thalamus. However, HIV-1 Tat decreased dendritic spine density of medium spiny neurons (MSNs) in the striatum, while also decreasing levels of the vesicular glutamate transporter VGLUT1, the main cortical input to MSN dendritic spines. Early morphological changes in the striatum have been previously reported and may lead to the decrease in VGLUT1 in the present study. To assess the effects of HIV-1 Tat and morphine on sociability and daily life behaviors, Tat(+) and Tat(-) mice were exposed to HIV-1 Tat for 8 weeks and administered saline or ramping doses of morphine twice daily (s.c.) during the last 2 weeks of HIV-1 Tat exposure. In the resident intruder test, HIV-1 Tat and morphine decreased aggressive social interactions; whereas HIV-1 Tat only decreased non-aggressive social interactions. Interestingly, when mice were placed in a novel environment HIV-1 or morphine did not affect social interaction suggesting that HIV-1 Tat-induced anxiety may mask behavioral changes in stressful environments. In home cages, HIV-1 Tat also decreased nest development; whereas morphine decreased burrowing indicating that HIV-1 Tat and morphine interfere with different behaviors of daily life. Together, these data suggest that HIV-1 Tat uniquely and systematically disrupts inhibitory and excitatory synapses throughout the cortico-basal ganglia-thalamo-cortical circuit and HIV-1 Tat and morphine mediate changes in sociability and daily life behaviors.

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Nanosymposium

632. HIV-Associated Neurocognitive Disorders

Location: Room S403

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 632.03

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH MH087332
NIH MH104131
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DA026306 (P5)

Title: Microglia-specific p38α knockout affects CNS gene expression *in trans*genic NeuroHIV model

Authors: *D. BHULLAR[1], R. MAUNG[1], U. IRFAN[1], D. OJEDA-JUÁREZ[1,2,3], M. KAUL[1,4,5]; [1]Univ. of California, Riverside, Riverside, CA; [2]Grad. Sch. of Biomed. Sciences,, [3]Infectious and Inflammatory Dis. Center,, Sanford Burnham Prebys Med. Discovery Inst., San Diego, CA; [4]Infectious and Inflammatory Dis. Center,, Sanford Burnham Prebys Med. Discovery Inst., San diego, CA; [5]Translational Methamphetamine AIDS Res. Ctr. (TMARC), Dept. of Psychiatry,, UCSD, San diego, CA

Abstract: HIV-1 infection of the central nervous system results in motor and cognitive defects in a significant number of individuals. Development of combined antiretroviral therapy (cART) has changed HIV to a chronic disease but low-level HIV protein expression inflammatory responses and neurodegeneration persist. The pathology of the infected brain is characterized by enhanced leukocyte infiltration, microglial activation, aberrant expression of inflammatory factors, neuronal loss and dysregulation, and blood-brain barrier disruption. Transgenic mice expressing HIV-1 coat glycoprotein gp120 in astroglial cells (HIVgp120tg) display neuropathological features similar to HIV dementia patients. The p38α mitogen-activated protein kinase (MAPK) regulates the biosynthesis of pro-inflammatory factors in endotoxin-stimulated and HIV-infected macrophages. In order to determine the role of microglial p38α signaling in HIV mediated neuronal injury, we cross-bred p38α floxed with CX3CR1 Cre HIVgp120-expressing mice resulting in a p38 knockout specifically in microglia and macrophages. Immunofluorescence studies on brain sections of the mice were used to compare HIVgp120tg brains with and without microglia-specific p38 knockout. Sagittal brain sections were stained for neuronal MAP2, pre-synaptic terminal protein synaptophysin, astrocytic GFAP and microglial Iba1. Astrocytic GFAP levels remained unaffected by microglial p38α deficiency. However, we observed a significant loss of MAP2 and synaptophysin levels compared to non-tg controls only in HIVgp120tg animals with p38-expressing microglia but not in HIVgp120-expressing brains with microglia-specific p38 knockout. The total number of microglia remained unaffected by the cell-specific

lack of p38 as indicated by counts of microglia. We also analyzed the RNA expression in the brains of these animals. Although most of the innate immune genes like Ccl2, Ccl3, Ccl4, Ccl5, Mx1, Cxcl10, Cxcl11 and Tnfα were unaffected, we found significant downregulation of genes like iNos, Irf3 and upregulation of Casp3 in microglial p38α deficient HIVgp120-expressing mice. Thus, our model confirmed a critical role of microglial p38 MAPK in the neurotoxicity and gene expression triggered by the HIV-1 gp120 protein.
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Nanosymposium

632. HIV-Associated Neurocognitive Disorders

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant RO1 DA02446
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Title: HIV and morphine induce GABAergic deficits through dysregulation of KCC2

Authors: *A. J. BARBOUR, A. R. MCQUISTON, P. E. KNAPP;
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Abstract: Despite the introduction of combined antiretroviral therapy, the CNS remains susceptible to insult from HIV-1 and inflammatory factors which cause sublethal damage to bystander neurons, providing the cellular basis of HIV-associated neurocognitive disorders (HAND). Opiate use is often comorbid with HIV infection and these patients show exacerbated HAND symptomology. Little is known about electrophysiological changes associated with HIV ± morphine co-exposure. We addressed this question by developing a dissociated primary human model derived from differentiating human neural progenitor cells (hNPC) into a mixed neuron - astrocyte culture containing glutamatergic and gamma-aminobutyric acid-(GABA)ergic neurons. Optical techniques were used for electrophysiological experiments, thus circumventing the biohazard of sharp electrodes in the presence of HIV. With genetically encoded voltage/calcium indicators (GEVI/GECI), Archon1 and GCaMP6f, we measured primary human neuron electrophysiological and calcium activity to elucidate changes in excitatory-inhibitory balance due to HIV ± morphine exposure. We determined that HIV and morphine both dysregulate neuronal $[Cl^-]_i$ resulting in hyperexcitability. K-Cl cotransporter 2 (KCC2) maintains low $[Cl^-]_i$ necessary for $GABA_AR$-induced hyperpolarization. Thus, we hypothesized that HIV and morphine decrease expression/activity of KCC2 leading to dysregulated $[Cl^-]_i$ and reduced

$GABA_AR$ mediated hyperpolarization. This was confirmed by immunostaining experiments that showed significant loss of KCC2 immunoreactivity in neurons exposed to supernatant from HIV-infected monocytes (125-500 pg/mL p24) and 500 nM morphine in the absence of neuron death. We have further determined that HIV-1 transactivator of transcription (Tat)-induced activation of NMDAR and glycoprotein 120 (gp120)-induced activation of CCR5 (novel mechanism of KCC2 regulation) are viral factors that mediate KCC2 loss. Mu opioid receptor antagonist reversed morphine effects. These results correlate with significant defects of GABA-ergic signaling in human neurons exposed to HIV, or HIV proteins ± morphine, as measured by Archon1 and GCaMP6f. KCC2 immunoreactivity and response to GABA were rescued by co-exposure with KCC2 activity enhancer, CLP257, or by targeting upstream pathways. We further examined KCC2 immunoreactivity in doxycycline-inducible astrocyte-specific HIV-Tat transgenic mice to examine if these changes occur in an *in vivo* model of HAND. Our data identify KCC2 and upstream activity as a promising, novel target for therapeutic intervention to alleviate functional changes underlying HAND ± opiate use.

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632. HIV-Associated Neurocognitive Disorders

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: R01 DA045588
DA018633

Title: Dynamic shifts in HIV-1 Tat-induced excitability and heightened sensitivity to morphine in dopamine D1 receptor-expressing striatal medium spiny neurons

Authors: *A. R. S. LARK[1], L. K. SILVA[1], W. D. MARKS[2], K. F. HAUSER[1];
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Abstract: Despite the advent of combination anti-retroviral therapies, 30-50% of HIV-infected individuals still exhibit neurocognitive disorders. The striatum appears to be especially vulnerable to HIV-1 infection, harboring high viral loads and exhibiting medium spiny neuron (MSN) damage—presumably leading to motor deficits that can occur with neuroHIV. Synaptodendritic injury in MSNs can be modeled via exposure to HIV-1 protein trans activator of transcription (Tat) and exacerbated by chronic co-exposure to opiates. Because HIV-infected individuals can develop intractable painful neuropathy that is often treated acutely with opiates, we also assessed the pathophysiological effects of acute opiate exposure in vulnerable neuronal

populations of the striatum. To discern the effects of Tat and acute opiates on the dopamine D1 and D2 receptor-expressing MSNs over time, we crossed *Drd1*-tdTomato or *Drd2*-eGFP lines with our transgenic murine HIV model: a doxycycline-inducible GFAP-driven HIV-1 Tat model. Whole-cell patch clamp recordings of MSNs were performed in *ex vivo* striatal slices to explore progressive deficits caused by Tat. Our data indicate that 48 h or 2-weeks Tat exposure significantly increased D2 MSN firing rates. By contrast, D1 MSNs showed initial 48 h increases, followed by a transient decrease (2 weeks), in firing rates in response to Tat—suggesting that D1 MSNs are highly plastic and uniquely vulnerable to Tat depending on the duration of exposure. At 2 months, we observed nearly complete elimination of the changes in firing seen at earlier time points. To further understand these changes, we then looked at shifts in interneuron populations and other alterations directly affecting MSNs. Acute morphine exposure increased D1 MSN firing rates irrespective of Tat and variably affected the response of D2 MSNs. Because few D2 MSNs express mu opioid receptors suggests that morphine's effects are independently mediated by glia or interneurons.

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Nanosymposium

632. HIV-Associated Neurocognitive Disorders

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Presentation Number: 632.06

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant R21ES025920
JHU R25MH080661-11

Title: Gut and blood-brain barriers in a rat model of methamphetamine abuse by HIV-infected humans

Authors: *M. OHENE-NYAKO, A. L. PERSONS, T. CELESTE NAPIER;
Rush Univ. Med. Ctr., Chicago, IL

Abstract: Disruption of the blood-brain barrier (BBB) and gut-mucosal barrier (GMB) causes inflammatory-mediated pathologies in HIV-infected individuals. Use of methamphetamine (meth) is prevalent in the HIV-infected population. Meth is known to alter the BBB, but its effect on the GMB, and the effects of HIV/meth comorbidity is under-studied. We revealed that HIV-1 transgenic (Tg) rats that self-administer meth have impaired hippocampal BBB (Ohene-Nyako *et al.*, *JNIP*, 2019) and a leaky colon (Persons *et al.*, *PLoS One*, 2018). The pathology of the BBB was associated with increased levels of matrix metalloproteinase-9 (MMP-9) in the Tg rats, and in non-Tg rats that administered meth. Evaluations of signaling pathways that regulate MMP-9 revealed that MMP-9 dysregulation by HIV-1 proteins and meth may involve NFκB but not

ERK. Here, we sought to determine if similar pathological features occur in the GMB, and we examined colon samples taken from Tg and non-Tg rats that self-administered meth (0.02-0.04mg/ 0.05ml/kg) 2h/day for 21 days (cumulative meth intake was 4.5±0.3 and 5.2±0.5mg/kg, respectively), and saline-yoked controls. One day following the last operant session, distal colon samples were harvested. Levels of MMP-9, NFκB and ERK were evaluated using immunoblotting. Two-way ANOVA revealed a main genotype effect for MMP-9 levels and the ratio of phosphorylated (activated) ERK to total ERK (pERK/ERK) to increase, and NFκB levels to decrease. *Post hoc* analyses revealed differences between saline Tg, and saline non-Tg rats. There was a consistent non-significant trend for MMP-9 and pERK/ERK to be increased by meth in non-Tg rats. As a collective, outcomes indicate a role for MMP-9 in both BBB and GMB pathology induced by HIV-1 proteins. Observations from ERK and NFκB suggest that HIV-1 protein-induced dysregulation of MMP-9 may occur *via* different signaling pathways in the brain and colon. Although no meth effects were significant in the gut, observed trends in the non-Tg rats suggest that with greater meth exposure, effects of the stimulant would emerge. Studies to establish mechanisms of HIV-1 protein (e.g., Tat)-induced colon barrier pathology are ongoing in colon cell (Caco-2) cultures.

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Nanosymposium

632. HIV-Associated Neurocognitive Disorders

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant DA039791
University of Mississippi, School of Pharmacy

Title: HIV-1 Tat and morphine promote neuroendocrine dysfunction that may involve disruption of mitochondrial complexes I and II

Authors: *J. J. PARIS, F. MAHDI, M. SALAHUDDIN, A. N. QRAREYA, Z. SHARIAT-MADAR;
BioMolecular Sci., The Univ. of Mississippi, University, MS

Abstract: Patients infected with human immunodeficiency virus type 1 (HIV-1) are at risk for neuroendocrine dysfunction. The incidence is increased among those with a history of opioid abuse; but, neuroendocrine interactions are complex and the targets involved are unclear. In mice, we have observed that expression of the HIV-1 regulatory protein, trans-activator of transcription (Tat), interacts with morphine to dysregulate formation of neurosteroids in the brain, which are dependent on mitochondria for *de novo* synthesis. Add-back of the

neuroprotective steroid, allopregnanolone (AlloP), ameliorates Tat/morphine-mediated behavioral pathology in mice and neurotoxicity in cell culture. Given that Tat is mitotoxic, we hypothesized that HIV-1 Tat and/or morphine would promote mitochondrial dysfunction that could be rescued by physiological concentrations of AlloP. HIV-1 Tat was conditionally-induced (or not) by doxycycline in Tat-transgenic mice (Tat+) and their control counterparts (Tat-). Tat+ and Tat- brain cells were digitonin-permeabilized, energized from mitochondrial complex I via malate/pyruvate or complex II via succinate, and assessed for oxygen consumption rate (OCR) via an Oxytherm Clark-type electrode. Tat expression significantly reduced basal OCR and attenuated succinate-driven increases. No changes were observed following antimycin A or ascorbate/TMPD. Mitoplasts were prepared from C57BL/6HNsd mouse brains and were assessed following direct exposure to HIV-1 Tat (100 nM), morphine (500 nM), and/or AlloP (10 nM). When energized from complex I, either morphine or AlloP increased basal OCR. Tat significantly decreased OCR and this was not further influenced by morphine; however, AlloP significantly reversed this effect. When energized from complex II, no effects of Tat or morphine were observed, but OCR was increased by AlloP. Treatments were recapitulated in digitonin-permeabilized human neuroblastoma cells (SH-SY5Y) with similar results; albeit, morphine and Tat were found to interact to reduce OCR when cells were energized from complex II. Formation of reactive oxygen species were likewise increased (~10%) by Tat in SH-SY5Y cells or mouse primary mixed glia and these effects were attenuated by AlloP (0.1-100 nM) in a concentration-dependent manner. Interestingly, morphine interacted in glia to reduce AlloP's protective efficacy. Thus, Tat may disrupt mitochondrial complexes I and II, with cell-type selective morphine interactions at complex II. Mitochondrial disruption seems likely involved in related neuroendocrine dysfunction and administration of a neurosteroid, such as allopregnanolone, may ameliorate deficits.

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Nanosymposium

633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

Location: Room N227

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 633.01

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Timing of decompression in cervical spinal cord injury

Authors: *B. AARABI[1,2], T. CHRYSSIKOS[1], G. SCHWARTZBAUER[1], C. SANSUR[1], K. SHANMUGANATHAN[1], N. AKHTARDANESH[2], J. SIMARD[1], N. CAFFES[1], J. OLIVER[1], M. SCARBORO[1];
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Abstract: Biologic rationale and preclinical studies indicate that when sustained compressive pressure on the spinal cord is relieved early, there is improved behavioral recovery in different experimental models. Preclinical studies carry with themselves bias and low level internal validity, making translational studies hard to interpret. A few low level clinical traumatic spinal cord injury (TSCI) studies have supported this concept suggesting early decompression of the spinal cord will improve motor and functional outcome. The therapeutic effect of surgery and its timing as neuroprotective measures in TSCI remain uncertain. Additionally, the relationship between timing of decompression, extent of decompression, imaging biomarkers evidence of injury severity, and outcome are incompletely understood. We investigated the effect of timing of decompression and long-term neurological outcome in patients with postoperatively confirmed decompression using CT and MRI imaging studies. Six months after cervical SCI, AIS grade conversion was determined in 72 AIS grades A, B, and C patients whose postoperative CT and MRI confirmed spinal cord decompression. Thirty-two patients underwent decompressive surgery less than 12 hours from injury, 25 within 12-24 hours, and 15 more than 24 hours after trauma. Age, gender, injury mechanism, intramedullary lesion length (IMLL) on MRI, admission ASIA motor score and surgical technique were not statistically different in-between groups. Motor complete patients (AIS A and B, p=0.009) and those with fracture dislocations (tear drop and locked facets, p=0.01) tended to be operated on earlier. One or more grade improvement was 55.6% in AIS grade A, 60.9% in AIS grade B, and 86.4% in AIS grade C patients. Admission AIS motor score (p=0.0004) and pre-operative IMLL (p=00001) were the strongest predictors of neurological outcome. AIS grade improvement was 65.6% in patients undergoing decompressive surgery within 12 hours after trauma, 60% in patients undergoing surgery within 12-24 hours, and 80% when decompression was performed more than 24 hours after injury (p=0.424). Multiple regression analysis of all significant and marginally significant variables revealed that the only significant variable predictive of AIS grade conversion to a better grade was IMLL (odds ratio 133.51, CI 11.68-1525.71, p<0.0001). In patients with postoperative CT and MRI confirmation of decompression following traumatic cervical SCI, pre-operative IMLL and not the timing of surgery appears to determine long-term neurological outcome.

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Nanosymposium

633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

Location: Room N227

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Presentation Number: 633.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: UCL MB/PhD programme scholarship supported by The Sackler Fund.

Title: Tissue engineering for spinal cord repair - Approaches to enhance olfactory ensheathing cell transplantation

Authors: *R. D. BARTLETT, V. ROBERTON, D. CHOI, J. B. PHILLIPS;
Univ. Col. London, London, United Kingdom

Abstract: Spinal cord injury affects between 250,000 and 500,000 new people each year. It may lead to severe disability and current treatments are limited. Transplantation of olfactory ensheathing cells (OECs) has demonstrated convincing efficacy in animal models of spinal cord injury and they can be safely harvested from human patients to facilitate autologous transplant. However, only 1% of OECs remain viable at the lesion site following transplantation and the spinal cord microenvironment lacks the structural guidance cues required for effective regeneration. Such factors limit the current effectiveness of OEC transplantation. This study aimed to improve the delivery of OECs using biomaterials and tissue engineering. Mechanical properties play a critical role in determining cellular behaviour, and so rat spinal cord tissue was first comprehensively characterised using compressive dynamic mechanical analysis. Thoracic spinal cord was found to be significantly stiffer than cervical and lumbar spinal cord tissue, although there were also small differences between cervical and lumbar spinal cord ($p<0.001$, $n = 18$). Within the cervical spinal cord, there was significant mechanical anisotropy ($n = 12$). Biomaterials suitable for clinical use and scalable for good manufacturing practice (GMP) production were selected and precisely tuned to mimic the mechanical properties of cervical spinal cord tissue. Collagen and fibrin hydrogel formulations were assessed for their ability to support OEC survival, where low concentration fibrin hydrogels conferred the highest survival of 85% ($p<0.001$, $n = 17$). Culture of OECs in 3-dimensional hydrogel environments also significantly increased the proportion of cells expressing a key repair marker ($p75^{NTR}$). Relative to monolayer culture, fibrin hydrogels increased the proportion of cells expressing $p75^{NTR}$ by approximately 3-fold and collagen hydrogels increased this by 4-fold ($p<0.001$, $n =24$). Following transplantation into a rat unilateral dorsal resection model of cervical spinal cord injury (Sprague-Dawley males, ≈200g), fibrin OEC hydrogels significantly improved forepaw posturing ($p=0.0198$, $n = 5$) and function ($p=0.005$, $n = 4$) relative to collagen OEC hydrogels at 14 days post-injury. In conclusion, tissue engineering approaches significantly enhanced the survival and phenotype of OECs, and cellular hydrogels with mechanical properties matched to spinal cord tissue correlated with improved functional recovery shortly after transplantation. Methods to align OECs *in situ* are now being explored to promote linear regeneration of damaged long-fibre tracts after injury.

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Nanosymposium

633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

Location: Room N227

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 633.03

Topic: C.11. Spinal Cord Injury and Plasticity

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The Ronald D. Deffenbaugh Family Foundation
NIH/NINDS R01 NS030853
T32 Neurological and Rehabilitation Sciences Training Program

Title: Inducing neural plasticity after spinal cord injury to recover impaired voluntary movement

Authors: *J. A. BORRELL[1,2], B. J. LAMB, Jr.[3,2], D. GATTOZZI[4], D. KRIZSAN-AGBAS[3], R. J. NUDO[5,2], S. B. FROST[5,2];
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Abstract: The purpose of this study was to determine if spike-triggered intraspinal microstimulation (ISMS) results in improved motor performance in an ambulatory rat model of spinal cord injury (SCI). Experiments were carried in adult, male, Sprague Dawley rats with 175 kdyn moderate T8 contusion injury. Rats were randomly assigned to one of two groups: Control or Activity Dependent Stimulation (ADS) therapy. Four weeks post-SCI, all rats were implanted with a recording electrode in the left hindlimb motor cortex and a fine-wire, custom-made stimulating electrode in the contralateral lumbar spinal cord. Intracortical and intraspinal microstimulation were used to find sites of similarly evoked hip movements, which were paired together for ADS therapy. In the ADS therapy group, spike-stimulus conditioning was administered for 4 hours/day, 4 days/week, for 4 weeks via a tethered cable in a testing chamber. During therapy sessions, single-unit spikes were discriminated in real time in the hindlimb motor cortex and used to trigger stimulation in the spinal cord ventral horn. The optimal stimulus intensity (50% ISMS movement threshold) and spike-stimulus delay (10ms) determined in preliminary anesthetized preparations were used during ADS. Control rats were similarly implanted with electrodes but did not receive stimulation therapy. Motor performances of each rat were evaluated before SCI contusion, once a week post-SCI for four weeks (prior to electrode implantation), and once a week post-conditioning for four weeks. Behavioral testing included BBB scoring, Ledged Beam walking, Horizontal Ladder walking, treadmill kinematics via the DigiGait and TreadScan system, and open field walking using OptiTrack kinematic analysis. BBB scores were significantly improved in ADS rats compared to Control rats after 1 week of therapy. In the ADS therapy rats, BBB scores were significantly improved after three weeks of ADS therapy when compared to pre-therapy ADS. Foot fault scores on the Horizontal Ladder were significantly lower in ADS rats compared to pre-therapy ADS and Control rats after 1 week of therapy. In addition, foot faults on the Horizontal Ladder returned to pre-injury measures after three weeks of ADS therapy. Foot fault scores on the Ledged Beam and kinematic analysis using the DigiGait and TreadScan system showed deficits after SCI in both ADS and Control rats but there were no significant differences between groups after 4 weeks of ADS therapy. These results show that activity dependent stimulation using spike-triggered ISMS can enhance

behavioral recovery of locomotor function, as measured by the BBB score and the Horizontal Ladder task after spinal cord injury.

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Nanosymposium

633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

Location: Room N227

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 633.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CSCR16ERG019

Title: Nanoscript-based non-viral transient repression of PTEN for axonal regeneration in the CNS

Authors: *S.-T. D. CHUENG[1], X. QIU[2], D. SUN[1], W. YOUNG[1], K. LEE[1];
[1]Rutgers Univ., Piscataway, NJ; [2]The Second Affiliated Hosp. of Xi'an Jiaotong Univ., Xi'an, China

Abstract: Spinal cord injury (SCI) results in devastating cellular dysfunctions that cause severe and permanent neurological deficits. Developing an effective and reliable therapeutic approach to treat spinal cord injury (SCI) is a difficult challenge for several reasons. First, the acute primary insult and secondary injury to the spinal cord cause central hemorrhagic necrosis and disruption of ascending and descending spinal tracts which communicate sensory and motor information to and from the brain. Second, subsequent gliosis at the injury site repairs the blood-brain barrier (BBB) can obstruct axon growth/regeneration and release inhibitory factors preventing axon regeneration. Third, adult neurons lose the capacity for continued axonal growth, through a genetic switch after the development has stopped. Given the intrinsically limited regenerative potential of the central nervous system (CNS) and the complex inhibitory SCI environment, there is a critical need for effective strategies to stimulate robust axon regeneration and neurite outgrowth to re-establish the damaged neural circuitry. To this end, we have developed a nanoparticle-based artificial transcription factor (NanoScript) capable of efficiently and selectively regulating the well-reported PTEN/mTOR pathway in a non-viral transient manner to promote axon growth and regeneration. We rationally designed the NanoScript platform to repress PTEN expression (NanoScript-PTEN) and evaluated the therapeutic effect of NanoScript-PTEN on SCI rehabilitation. We hypothesized that the efficient repression of PTEN expression would lead to upregulation of mTOR and therefore promoted regeneration of axons at the spinal injury site. The NanoScript platform replicates the multi-domain structure of natural TF proteins and emulates the gene-regulating function of TFs. Most

importantly, we believe NanoScript can provide a safe and efficient gene manipulation method that will accelerate efforts for axonal regeneration and ultimately functional recovery of spinal cord injury.

Disclosures: S.D. Chueng: None. **X. Qiu:** None. **D. Sun:** None. **W. Young:** None. **K. Lee:** None.

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633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

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Presentation Number: 633.05

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Vascular endothelial growth factor: Molecular target of trans-spinal direct current stimulation (tsDCS)

Authors: *S. SAMADDAR, Z. AHMED;
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Abstract: Trans-spinal direct current stimulation (tsDCS) is a non-invasive powerful tool demonstrated to positively affect behavior and motor function. tsDCS causes immediate and long-term effects in spinal excitability (Ahmed, 2011, 2013; Ahmed and Wieraszko, 2012; Cogiamanian et al., 2011, 2012). Our goal is to use tsDCS to ameliorate the devastating effects of CNS injuries on motor function. Though researchers have been successful in improving motor function using tsDCS, the molecular basis of its effects remains unknown. Our study objective is to investigate the effect of tsDCS on Vascular Endothelial Growth Factor (VEGF) in SCI-injured and SCI-non-injured animals. VEGF seems to have a role in development of allodynia and non-specific sprouting of myelinated axons following SCI (Nesic et al., 2010). We used 7 experimental groups: non-SCI-injured-non-tsDCS control group, Sham-tsDCS group, cathodal-tsDCS-non-injured group, anodal-tsDCS-non-injured group, sham-tsDCS-SCI-injured group, cathodal-tsDCS-SCI-injured group, and anodal-tsDCS-SCI-injured group. Stimulation paradigm includes single session stimulation, and repeated stimulation. Our initial findings suggest an upregulation of VEGF following Cathodal tsDCS and downregulation following Anodal tsDCS. Preliminary data from the VEGF mRNA levels have also shown upregulation after Cathodal tsDCS. These findings will help us understand molecular mechanisms triggered by tsDCS and its effects on neuronal tissue.

Disclosures: S. Samaddar: None. **Z. Ahmed:** None.

Nanosymposium

633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

Location: Room N227

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 633.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NYSCIRB , C33278GG

Title: Transplantable neural circuitry for spinal cord injury

Authors: Z. T. OLMSTED[1], C. STIGLIANO[3], J. CIBELLI[4], P. J. HORNER[3], *J. L. PALUH[2]; [1]Nanobioscience, [2]SUNY Polytechnic Inst., Albany, NY; [3]Ctr. for Neuroregenerative Med., HMRI, Houston, TX; [4]Animal Physiol., Michigan State Univ., East Lansing, MI

Abstract: Human stem cell-derived neuronal and glial cells have potential to restore damaged circuitry of the injured spinal cord. However, current challenges in cell delivery, cell survival and host tissue integration must first be resolved. Our goal is to generate fully characterized cells and circuitry for transplantation into the damaged spinal cord using neural-encapsulated microribbons, while also optimizing cell delivery methods and manipulation of the SCI microenvironment to remove inhibitory signals. Encapsulated are spinal cord neural stem cells (scNSCs) or brachial spinal motor neurons (SMNs) plus oligodendrocyte progenitor cells with or without chondroitinase ABC (chABC). To generate cells for encapsulation and transplantation, we use the induced pluripotent stem cell (hiPSC) line F3.5.2. scNSCs with brachial regional identity have characteristic hallmarks of multipotency and neurosphere formation. SMNs generated from scNSCs are capable *in vitro* of forming synaptic networks, innervating rodent myotubes, and exhibit active mitochondrial transport in neurites. Encapsulated scNSCs retain robust viability and differentiation potential upon recovery as assessed by neurogenesis and maturation (synaptogenesis) even following long-term shipping at 37°C (From Albany, NY to Houston TX). Microribbon composition and parameters have been evaluated and the encapsulated SMNs can be induced to exhibit axon outgrowth perpendicular to ribbons or along the length of microribbons to optimize appropriate recovery outcomes. The formation of neural circuits within the microribbons including synapse formation is demonstrated. In summary we show that alginate microribbons offer a tunable and reproducible platform for delivery of therapeutic neural cells, retention of cell viability, injury site modification and capability for circuitry reformation. This work is funded by the NY State Spinal Cord Injury Review Board (NYSCIRB): “Healing the Contusion Injured Spinal Cord Microenvironment with Nanotechnology and Stem Cells”.

Disclosures: Z.T. Olmsted: None. **C. Stigliano:** None. **J. Cibelli:** None. **P.J. Horner:** None. **J.L. Paluh:** None.

Nanosymposium

633. Spinal Cord Injury: Non-Pharmacological Therapeutic Strategies

Location: Room N227

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 633.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Shaw Foundation

Title: Pediatric constraint induced movement therapy for children with brachial plexus injury: Cognitive, upper and lower extremity function changes

Authors: *T. KARAKOSTAS[1], E. KING[2], S. HSIANG[3];
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Abstract: In the past we reported immediate and long term upper and lower extremity function changes from a pediatric constraint induced therapy (pCI) camp for children with brachial plexus injury (BPI). The objectives of this study were to a) augment our results with cognitive changes, b) determine potential corticoplasticity related effects, and c) determine retention of these effects. This is a randomized control study including 17 children with BPI, 3-7 years of age, 9 of them randomly assigned in the experimental group. No participant had history of other neuromusculoskeletal injury or previous CI exposure. All subjects could use the affected arm as gross assist during play and self care tasks. Cognitively, they could follow two step commands. Treatment took place at a Children's Hospital.
We delivered 30 hours of treatment (3 hours of treatment specific training over 10 days). Activities focused on gross, fine motor and self feeding skills. Control group participants had traditional occupational therapy. Outcomes were measured using the Shrinner Hospital Upper Extremity Evaluation (SHUEE), the GAITRite to assess gait and a cognitive task to assess cognitive age. Experimental group participants were tested pre, post and 6 months post pCI. Results were initially explored with discriminant analysis and then for simplicity and reporting with t-tests ($a<0.05$). This report focuses on the experimental group performance.
Table 1 presents selected results based on the SHUEE the GAITRite and cognitive task that showed significant changes between pre and post pCI.
Table 1. Means, standard deviations and p values for selected output parameters.

Parameter	Pre	Post1	p	Post2	p
	Mean(SD)	Mean(SD)		Mean(SD)	(Post1 vs. Post2)
Spontaneous Functional Analysis	32.37(4.50)	38.75(4.71)	.01	33.00(6.19)	.08
Dynamic Positional Analysis	45.50(8.60)	57.25(6.49)	.0004	54.87(6.19)	.28
Velocity (normalized)	3.57(.80)	3.96(.69)	.02	4.02(.67)	.81

Cadence (normalized)	293.56(30.22)	313.37(27.36)	.01	328.63(30.43)	.16
Step length difference (cm) (involved vs. uninvolved)	0.98(.34)	0.50(0.40)	.02	0.62(.65)	.59
Cognitive age (normalized)	95.5(1)	99.3(2)	.02	101(2)	.18

This is, to our knowledge, the first randomized control study investigating the long term effects of pCI on motor an cognitive function of children with BPI. The results demonstrate clear improvements in the cognitive and upper and lower extremity function. Although gains are being retained after 6 months, it appears that lower extremity gains are better retained, while cognitive gains continue to improve.

Disclosures: T. Karakostas: None. **E. King:** None. **S. Hsiang:** None.

Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.01

Topic: D.03. Somatosensation – Pain

Title: Activators of two-pore-domain potassium channels as novel treatments for pain and migraine

Authors: *P. D. WRIGHT;
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Abstract: Two-pore domain potassium channels (K2Ps) carry background (or leak) potassium current and primarily act to maintain resting membrane potential. Genetic and functional evidence has pointed to roles for multiple K2P channels in pain and migraine and K2Ps are known to be expressed in sensory neurons. Activators of K2Ps are therefore likely to be of therapeutic benefit. However, K2Ps have proved difficult to modulate with small molecules and there is a lack of selective pharmacological tools which target them. This has limited investigation of the precise physiological function of individual K2Ps and efforts to generate K2P targeting therapeutics. We developed a cell-based system to identify novel activators across the K2P superfamily. An important part of this was to initially determine which K2P channels were amenable to activation (which channels were ‘druggable’). A novel cell-based thallium flux assay was developed, which optimized cell culture techniques to significantly reduce assay development times and screen multiple targets at once. Importantly our system was also designed and optimized for the identification of activators. This was then used to screen a library of FDA approved molecules and a subset of the LifeArc proprietary compound library. Our assay platform also allowed the simultaneous analysis of multiple channels for small molecule

selectivity. Novel activators were identified across a range of targets. Analogues were designed and synthesised to improve potency and efficacy of lead compounds. Comparisons of activators is complex due to differences in potency, efficacy and activity to known standards. Strategies to characterize selectivity of compounds across the broader superfamily will be discussed. Activators were also screened using automated patch-clamp techniques and activity was confirmed in this system. A subset of compounds was also screened to confirm activity in whole-cell patch clamp electrophysiology. It is hoped the compounds discovered will provide tools to be used in target validation studies and help to elucidate further the roles of individual K2P channels in neuroexcitability. The compounds identified may form the starting points for K2P targeting drug discovery programs and potentially allow the identification of new therapies for migraine and pain.

Disclosures: **P.D. Wright:** A. Employment/Salary (full or part-time):; LifeArc.

Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.02

Topic: D.03. Somatosensation – Pain

Support: NIH Grant F32NS100404
NIH Grant 5R35NS105076

Title: Single-cell transcriptional profiling of peripheral somatosensory neurons in animal models of neuropathic pain

Authors: *I. TOCHITSKY[1], W. RENTHAL[2], Y.-C. CHENG[5], L. YANG[3], M. E. GREENBERG[4], C. J. WOOLF[6];
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Abstract: Summary: Peripheral neuropathy initiates a massive transcriptional program associated with both pain and regeneration in peripheral somatosensory neurons, but the heterogeneity of these neurons has previously complicated the study of transcriptional changes in different cell types. By taking advantage of recent advances in single-cell transcriptomics, we have characterized the transcriptional changes induced in different neuronal and non-neuronal cell types after peripheral nerve injury and how these changes progress over time.
Aims: Characterize the cell-type-specific patterns of gene expression in mouse dorsal root ganglia (DRG) neurons and the transcriptional changes that occur in these cell types after nerve injury.

Methods: Single-nucleus RNA sequencing was performed on DRGs from naïve or injured C57/Bl6 mice at multiple time points after nerve injury or chemotherapy treatment. Neuronal and non-neuronal cell types were identified by clustering analysis and known marker gene expression. Marker gene expression data was confirmed by multiplex RNAScope in situ hybridization.
Results: Within hours after axotomy, all injured DRG neuron subtypes initiate a conserved injury-induced transcriptional program that ultimately generates novel and transcriptionally distinct neuronal cell states that lack many traditional neuronal cell type markers. The axotomy-induced transcriptional program is largely similar across nerve injury models but distinct from that generated by chemotherapy treatment. In neuropathy models such as sciatic nerve crush, injured neurons slowly recover/regenerate and the injured cell clusters disappear over several months, mirroring the time course of functional recovery. Genetic disruption of the injury-induced transcriptional programs delays functional recovery after sciatic nerve crush.
Conclusions: Single-cell RNA sequencing enables the molecular characterization of peripheral neuropathy in all the different subtypes of somatosensory neurons as well as non-neuronal cells. This transcriptomic dataset is a rich resource for studying neuropathy-induced gene expression changes and how these transcriptional changes contribute to neuropathic pain and neuronal regeneration.

Disclosures: I. Tochitsky: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nocion Therapeutics. **W. Renthal:** None. **Y. Cheng:** None. **L. Yang:** None. **M.E. Greenberg:** None. **C.J. Woolf:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nocion Therapeutics.

Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.03

Topic: D.03. Somatosensation – Pain

Title: Single cell RNA seq of a model of rodent nerve injury: A comprehensive resource for the exploration of cellular interactions underlying the emergence and persistence of neuropathic pain

Authors: *D. LOVATT[1], A. TAMBURINO[1], R. SANOJA[1], A. KRASOWSKA-ZOLADEK[1], L. LI[2], K. ZHANG[3], K. Q. TANIS[1], V. PETERSON[2], X. WANG[1], J. M. USLANER[1]; [1]Merck & Co., Inc.,, West Point, PA; [2]Merck & Co., Inc.,, Boston, MA; [3]Merck & Co., Inc.,, Boston, PA

Abstract: Peripheral neuropathic pain is caused by injury or disease to the peripheral somatosensory system resulting from frank injury, such as from amputation, as well as from

several pathological conditions, including diabetes mellitus, herpes zoster, and chemotherapy treatments for cancer. Following nerve injury, several cellular nerve repair and regeneration programs are triggered with distinct temporal patterns involving cells of the nervous, vascular and immune systems. However, the cell types and their intercellular signaling pathways that underlie nerve repair and the emergence and persistence of neuropathic pain in the wound microenvironment remain poorly understood**.** Thus, a better understanding of these cells and how they interact could help improve therapies for pain management.
Here, we used 10x Genomics single-cell RNA-sequencing (scRNA-seq) to elucidate the cellular components of injured nerve tissue and their paracrine signaling pathways in the chronic constriction injury (CCI) model of neuropathic pain in rat. We surgically extracted naïve nerves as well as neuromas at 3 days, 12 days and 60 days post-injury and enzymatically dissociated them into single-cell suspensions for scRNA-seq profiling. This yielded more than 77,000 individually profiled cells across all timepoints with high quality transcriptomes. Dimensional reduction, using t-SNE plotting followed by cell type marker analysis, revealed the presence of several distinct cell types identified as Schwann cells, macrophages, endothelial cells, vascular smooth muscle cells, mesenchymal cells, pericytes, dendritic cells, and T cells. Interestingly, several novel cell subtypes emerged as early as 3 days after injury. This included a population of non-proliferating dendritic cells as well as proliferating macrophages, mesenchymal cells and Schwann cells. Further, we extracted cell-cell signaling data to investigate the paracrine signaling pathways induced within the injured nerve and identified numerous paracrine and autocrine ligand-receptor pairs with temporal expression patterns not present in naïve nerve. These findings clearly demonstrate that the cellular heterogeneity of the nerve microenvironment increases significantly following injury and during nerve regeneration.
This work forms a comprehensive resource for further exploration and provides an unprecedented window into the elucidation of cellular interactions underlying the emergence and persistence of neuropathic pain associated with nerve injury.

Disclosures: **D. Lovatt:** None. **A. Tamburino:** None. **R. Sanoja:** None. **A. Krasowska-Zoladek:** None. **L. Li:** None. **K.Q. Tanis:** None. **V. Peterson:** None. **X. Wang:** None. **J.M. Uslaner:** None. **K. Zhang:** None.

Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.04

Topic: D.03. Somatosensation – Pain

Support: NIH K08 NS079482
NIH/NINDS: 1 R01 NS104295-01

Title: Mas-related G protein-coupled receptor D as a potential therapeutic target for painful diabetic neuropathy

Authors: *D. S. GEORGE[1], N. D. JAYARAJ[1], D. REN[2], A. BELMADANI[2], S. HACKELBERG[3], R. J. MILLER[5], D. M. MENICHELLA[4];
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Abstract: Diabetes is a major global health problem and about 25% of these patients develop painful diabetic neuropathy (PDN), a debilitating complication of diabetes. In patients with PDN, nociceptors within the dorsal root ganglion (DRG) become hyperexcitable and eventually degenerate. Despite the prevalence of the disease, the pathogenesis of the disease is unclear. Our overall aim is to identify changes in the gene expression profile in PDN pathology for the discovery of novel druggable targets. To specifically study changes to the nociceptive neurons in PDN, we used a molecular marker, Nav1.8 which labels about 90% of the nociceptive population. Deep RNA sequencing of the Nav1.8-Cre; Td-TomatoAi9 mice fed a regular (RD) or a high-fat diet (HFD) for 10 weeks identified 58 overexpressed and 360 underexpressed genes in HFD. We observed overexpression of several GPCRs, including the Mas-related G protein-coupled receptor D (Mrgprd), a gene implicated in neuropathic pain. Mrgprd+ neurons are a subset of the Nav1.8 population and interestingly, we discovered several of the candidate genes clustered to the Mrgprd subpopulation, indicating a functional role of Mrgprd and associated genes in the pathogenesis of PDN. To further study changes in Mrgprd expression, we used Mrgprd-EGFP mice. Mrgprd neurons are unmyelinated and do not express the neurofilament-200 (NF200), a, marker of myelination. Interestingly, we observed Mrgprd expression within a population of NF200+ neurons in the DRG of diabetic mice suggesting possible plasticity in a disease condition. Our previous work has shown that there is a significant reduction in the Nav1.8 intra-epidermal nerve fibers in the glabrous skin starting at six weeks on diet. Interestingly, a higher percentage of Mrgprd+ fibers, compared to Nav1.8+ fibers, in the skin (in particular in the dermis) of diabetic mice suggesting a possible role of Mrgprd+ fibers in the transmission of the painful stimuli. The identity of this population of DRG neurons remains to be investigated. Currently, efforts are directed towards the single cell gene expression analysis of the DRG population in RD and HFD mice to tease out this plasticity. Overall, we propose Mrgprd as a viable target for the development of disease-modifying therapeutics for PDN.

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Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.05

Topic: D.03. Somatosensation – Pain

Support: FAPESP GRANT 2013/08216-2

Title: Dendritic cells-expressing IDO-1 play a crucial role in the maintenance of neuropathic pain

Authors: *T. M. CUNHA[1], G. SOUZA[2], A. MAGANIN[2], M. M. FONSECA[2], A. DAGOSTIN[2], R. LEAO[2], J. O'CONNOR[3], F. CUNHA[2], J. ALVES-FILHO[2];
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Abstract: Aim of Investigation: Neuropathic pain, which is triggered by damage or disease of the somatosensory system, is one of the most important types of chronic pain. Nevertheless, critical pathophysiological mechanisms that maintain neuropathic pain are poorly understood. In the present study, the role of kynurenine metabolic pathway in the maintenance of neuropathic pain was investigated. **Methods:** Neuropathic pain was induced in C57BL6, indoleamine 2,3-dioxigenase-1 (*Ido1*$^{-/-}$)and 3-hydroxyanthranilate 3,4-dioxygenase (*Haao*$^{-/-}$)mice by peripheral nerve damage (Spared nerve Injury model, SNI). Mechanical allodynia was measured using von Frey filaments test. **Results:** We observed that the neuropathic pain is abrogated when the kynurenine (kyn) metabolic pathway is ablated pharmacologically or genetically. Mechanistically, peripheral upregulation of indoleamine 2,3-dioxigenase in dendritic cells leads to a systemic increase in levels of kyn. Kyn is transported to the spinal cord where it is metabolized by astrocytes-expressed kynurenine-3-monooxygenase. Ultimately, 3-hydroxyanthranilate 3,4-dioxygenase-derived quinolinic acid is responsible for the activation of glutamatergic NMDA receptor. In conclusion, these data reveal a previously unappreciated role for the kynurenine metabolic pathway as a critical link between peripheral immune system activation, spinal cord glia cells (astrocytes) and neuronal sensitization to maintain neuropathic pain. This novel paradigm offers potential new targets for drug development against this type of chronic pain.

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Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.06

Topic: D.03. Somatosensation – Pain

Title: A novel approach to visceral diabetic neuropathy

Authors: *R. DEBIAN[1], W. NAJJAR[1], N. LAWAND[1], A. EID[2], E. D. AL-CHAER[1];
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[2]Dept. of Anatomy, Cell Biol. & Physiological Sci., American Univ. of Beiruterican Univ. of Beirut, Bliss, Lebanon

Abstract: Visceral pain has been commonly correlated with patients suffering from diabetes mellitus (DM). Interestingly, most of the work done on visceral pain in diabetic models did not reveal the underlying mechanisms that contribute to the sensory disturbances of the disease. In this study, we explored visceral pain associated with type 2 DM (T2DM) in male diabetic rats. Moreover, we delineated the underlying inflammatory molecular and behavioral mechanisms by which diabetes can alter sensory aspects of the visceral organs.
Diabetes was established in rats through intravenous Streptozotocin (STZ) injections. They where then divided into two groups between control and diabetic. Behavioral tests were performed prior to and after diabetes establishment. 8 weeks after the establishment of diabetes, the control and the diabetic groups were then divided between rats injected with 40% 2,4,6-trinitrobenzene sulfonic acid (TNBS,Sigma) dissolved with 50% ethanol and rats injected only with ethanol. TNBS was mainly used in order to induce colon inflammation. Glucose levels and body weight were examined on a weekly basis. Behavioral tests followed by sacrifice were preformed to all four groups, at 1, 2 and 4 weeks after TNBS injection. The spinal cord, dorsal root ganglia and colon were harvested for histological staining to mark apoptosis and check for neuronal markers.
Symptoms of diabetes and inflammation were manifested in all rats with TNBS and STZ injections. Rats with T2DM suffering from sensory disturbances were characterized by significant hypersensitivity as evident in the behavioral results. Caspase 3, however, was prominent in all rats that had a TNBS injection mimicking a diabetic appearance. These findings suggest that diabetes is altering markers, inducing hypersensitivity and increasing the apoptosis of the cells at the level of the colon.

Disclosures: **R. Debian:** Other; Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut. **W. Najjar:** Other; Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut. **N. Lawand:** Other; Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut., Department of Neurology. **A. Eid:** Other; Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut. **E.D. Al-Chaer:** Other; Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut..

Nanosymposium

634. Novel Insights Into Neuropathic Pain

Location: Room S104

Time: Wednesday, October 23, 2019, 8:00 AM - 9:45 AM

Presentation Number: 634.07

Topic: D.03. Somatosensation – Pain

Support: UB-Mark Diamond Research Fund (ZL)
PAS-UBF-Experimental Neurology Fund (TAI)

Title: Perispinal targeting of brain tumor necrosis factor-alpha is antinociceptive for ongoing and evoked pain in rats with chronic constriction injury

Authors: *T. A. IGNATOWSKI[1], Z. M. LAMACCHIA[1], A. H. ABIDI[1], M. JAFFARI[1], T. AHMED[1], N. SINGH[1], E. L. TOBINICK[2], M. GHANDILI[1], R. N. SPENGLER[3];
[1]Dept. of Pathology and Anatom. Sci., Univ. at Buffalo, SUNY, Buffalo, NY; [2]Inst. of Neurolog. Recovery, Boca Raton, FL; [3]NanoAxis LLC, Clarence, NY

Abstract: Neuropathic pain is chronic pain that follows neuronal injury, mediated in the brain by elevated levels of the cytokine tumor necrosis factor-alpha (TNF). We have shown that peripheral nerve injury increases TNF in the hippocampus (pain perception region), which is both sufficient and required for the onset of neuropathic pain symptoms. Excess TNF also dysregulates neurotransmission in the hippocampus, which would alter connectivity with corticolimbic regions that process the sensory and emotional components of pain. In this study, we determined whether targeting excess brain TNF through perispinal delivery of a TNF antibody (TNFab) would be antinociceptive, and if there was an effect on pain perception. Male (n=23) and female (n=9) Sprague-Dawley rats weighing 175-250 g were used for these studies. Rats received either unilateral sciatic nerve chronic constriction injury to induce neuropathic pain or a control sham surgery. Thermal hyperalgesia was monitored every other day post-surgery. On day-8 post-surgery, rats were blindly randomized into groups that received a perispinal injection of a TNFab, control IgG isotype antibody, or the positive control group that did not receive perispinal treatment. The affective component, or perception of pain was assessed using conditioned place preference (CPP) to analgesia. Rats experiencing pain were conditioned by being confined in one of three chambers having specific sensory and tactile cues after an injection of saline, and then being confined in a different chamber following injection of amitriptyline (10 mg/kg, i.p.), a known analgesic. Rats that formed a preference for the amitriptyline-paired chamber have formed a CPP. Sham-operated rats administered amitriptyline did not develop a CPP. We found that CCI rats given the perispinal TNFab injection on day-8 post-surgery experienced alleviation of thermal hyperalgesia the day following the injection and on the final experiment day (Day 8 vs 9_{PreAmi}, $p < 0.001$; Day 8 vs 10, $p < 0.001$; 2-way RM ANOVA), and did not form a CPP to amitriptyline, due to TNFab-induced alleviation of pain. Rats given the perispinal IgG antibody only had acute alleviation of pain following amitriptyline injection (Day 8 vs $9_{PostAmi,}$ $p < 0.001$) and did form a CPP to amitriptyline (IgG Pre vs Post, $p = 0.056$). Our results reveal that perispinal administration of a TNFab inhibits the perception of pain associated with neuropathic pain. These findings provide proof-of-concept for an alternative analgesic target: TNF specifically in the brain. This is vital given the current, national opioid epidemic and imminent need of relief from chronic pain.

Disclosures: **T.A. Ignatowski:** None. **Z.M. LaMacchia:** None. **A.H. Abidi:** None. **M. Jaffari:** None. **T. Ahmed:** None. **N. Singh:** None. **E.L. Tobinick:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Institute of Neurological Recovery. **M. Ghandili:** None. **R.N. Spengler:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.01

Topic: D.05. Olfaction and Taste

Support: NIH Grant 106018
NIH Grant 107970

Title: Biased randomness, a connectivity mechanism for associative brain centers

Authors: K. ELLIS[1], E. AMEMATSRO[2], ***S. J. CARON**[2];
[2]Sch. of Biol. Sci., [1]Univ. of Utah, Salt Lake City, UT

Abstract: Uncovering fundamental mechanisms of neuronal connectivity that enable associative brain centers to learn efficiently is an important goal of neuroscience. In the *Drosophila* mushroom body, the constituent Kenyon cells receive input from olfactory projection neurons. Each projection neuron connects to one of the fifty-one glomeruli in the antennal lobe, the primary olfactory processing center. We and others have shown that these connections are unstructured in that there are no sets of glomeruli converging preferentially onto a given Kenyon cell. However, we found that the glomeruli are not represented with equal frequency among Kenyon cell inputs. Overrepresented glomeruli form many more connections than expected under a uniform distribution of inputs, whereas underrepresented glomeruli form far fewer connections than expected. We hypothesize that this non-uniform distribution, which we termed 'biased randomness', serves an important biological function, namely to predispose the ability of the mushroom body to represent certain ethologically pertinent odors. We are testing this hypothesis using two different strategies. First, using a mathematical model of the mushroom body as well as *in vivo* calcium imaging, we can demonstrate that, although biases do not affect the way most odors are represented in the mushroom body, they do affect the way a few ethologically pertinent odors are represented. These odors are detected by only one glomerulus. Odors detected by an underrepresented glomerulus fail to activate Kenyon cells. In contrast, odors detected by an overrepresented glomerulus activate large ensembles of Kenyon cells, similar in size to the ensembles activated by odors detected by many glomeruli. Second, we are determining whether and how the biases in Kenyon cell connectivity we detected in *Drosophila melanogaster* shift across closely related species. We, therefore, mapped the Kenyon cell inputs in *Drosophila sechellia*, a species that feeds exclusively on Morinda fruit. We observe that,

although most biases are conserved in both species, some biases shift significantly. We found that the glomeruli that show the largest shifts detect odors that have different ethologically meaning in each species. Altogether, our work supports the idea that 'biased randomness' is a wiring mechanism that predisposes associative brain centers to learn efficiently.

Disclosures: S.J. Caron: None. **K. Ellis:** None. **E. Amematsro:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.02

Topic: D.05. Olfaction and Taste

Title: Adult born neurons improve odor discrimination by mitral cells

Authors: *H. SHANI NARKISS, A. VINOGRAD, G.-I. TASAKA, N. YAYON, I. D. LANDAU, S. TERLETSKY, M. GROYSMAN, H. I. SOMPOLINSKY, A. MIZRAHI;
The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Adult-born neurons (abNs) are continuously generated in the sub ventricular zone, from which they migrate and integrate into the olfactory bulb circuitry. The role of abNs in odor processing has remained unknown, in part due to technical limitations in targeting these neurons with reasonable efficiency for causal manipulations. We show that a Nestin-CreER2 driver system with a newly developed mice expressing histone-BFP as a reporter and tTA2 for additional genetic manipulation is highly efficient and specific in labeling and genetically accessing abNs. Using this genetic system, we induced expression of an inhibitory DREADD for temporarily silencing abNs. Using *in vivo* two-photon imaging in awake head-restrained mice, we compared the responses of mitral cells to a panel of 11 odors (6 monomolecular and 5 natural odors), before and after silencing of their presynaptic abNs. Surprisingly, we found a strong but paradoxical effect on mitral cell responses when silencing inhibitory abNs: while excitatory odor-responses were inhibited, inhibitory odor-responses were weakened. As our system allows us to track and manipulate the exact same neurons at different time points, we measured the effects of silencing abNs at different age points. Interestingly, the effects were limited to abNs that were ~1-2 months old, waning off as they matured. Computational analysis demonstrates that silencing abNs within the first month of age decreases the ability of mitral cells to discriminate odors. A network model of the OB reproduces these results and suggests a circuit phenomenon that underlies the role of abNs. Together, these data explain how a small population of abNs contribute to enhanced odor discrimination by mitral cells.

Disclosures: **H. Shani Narkiss:** None. **A. Vinograd:** None. **G. Tasaka:** None. **N. Yayon:** None. **I.D. Landau:** None. **S. Terletsky:** None. **M. Groysman:** None. **H.I. Sompolinsky:** None. **A. Mizrahi:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.03

Topic: D.05. Olfaction and Taste

Support: NIH Grant R01 DC014453
NIH Grant F32 DC015938

Title: Odor mixture coding in mouse olfactory receptor neurons

Authors: ***J. D. ZAK**[1], G. REDDY[2], M. VERGASSOLA[2], V. N. MURTHY[1];
[1]Mol. & Cell. Biol., Harvard Univ., Cambridge, MA; [2]Physics, UCSD, San Diego, CA

Abstract: The odor landscape is a complex blend of discrete molecules that each activate unique, yet highly overlapping, populations of olfactory receptor neurons (ORNs). Despite a rich diversity of ORN subtypes (~1200 in mouse and ~400 in humans), the overlapping nature of odor inputs may lead to saturation of neural responses, which could be mitigated by normalizing mechanisms at the early stages of stimulus encoding. A potential mechanism to accomplish normalization is competitive antagonism at the level of receptor-ligand binding in the olfactory epithelium. Our prior theoretical work (Reddy, Zak et al., 2018) demonstrates that if ORN activation occurs through a multistep pathway where ligand binding and G-protein activation are decoupled, antagonistic interactions between odor molecules in a mixture may be readily observed. These antagonistic interactions may thereby provide a mechanism to normalize input to the olfactory system without the need for recurrent circuitry or lateral interactions between glomeruli. Prior experimental studies have described non-linear interactions resulting from odor mixtures; however, it remains unknown whether antagonism is a central feature of how odor information is encoded by receptor neurons. We have begun to investigate odor mixture interactions, with a focus on antagonism, in live, freely breathing mice. We used multiphoton microscopy to visualize odor responses of ORNs expressing the calcium indicator GCaMP3. We first imaged responses of ORN axons in the glomerular layer of the olfactory bulb. We extracted calcium signals from 296 unique glomeruli from nine mice using two separate pairs of odors at concentrations that spanned four orders of magnitude. We used two different odor pairs, one that activated highly overlapping set of glomeruli and another that activated discrete glomerular patterns in the olfactory bulb. The mean Euclidean distance in activity pattern for pair one was 0.35±0.05, and 1.48±0.12 for pair two ($p < 0.0001$, rank-sum test). In our dataset, we frequently observed antagonistic interactions in both odor pairs that were predicted by our model. We could

not, however, rule out the possibility that these interactions arise through lateral inhibition in the glomerular layer. To exclude this possibility, we have developed a method that allows for direct optical access to receptor neuron cell bodies within the olfactory epithelium, where we have imaged >500 cells. The ability to study mixture interactions in ORNs in their native environment offers new avenues for linking odor encoding in the periphery to olfactory perception in a tractable animal model.

Disclosures: **J.D. Zak:** None. **G. Reddy:** None. **M. Vergassola:** None. **V.N. Murthy:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.04

Topic: D.05. Olfaction and Taste

Support: NIH R01NS109961

Title: Mapping olfactory codes to perceptual spaces with synthetic optogenetic odors

Authors: *E. CHONG[1], M. MORONI[2,3], C. WILSON[1], S. SHOHAM[1], S. PANZERI[2], D. RINBERG[1];
[1]NYU Neurosci. Inst., New York, NY; [2]Inst. Italiano Di Technologia, Revereto, Italy; [3]Ctr. for Mind and Brain Sci. (CIMeC), Univ. of Trento, Trento, Italy

Abstract: Advances in monitoring and modeling population neural activity have revealed tremendous complexity in neural codes. However, understanding how code features are consequential to animal behavior, remains challenging. We developed a novel experimental approach and accompanying theoretical framework within mouse olfaction, where odors evoke dynamic, spatio-temporal olfactory bulb activity. We trained mice to recognize synthetic 'odors' constructed from precise, parametrically-defined optogenetic stimulation patterns, and measured perceptual changes during controlled spatio-temporal shifts within these patterns. We examined changes along spatial or temporal dimensions and developed a data-driven mathematical model of how various spatial and temporal features are jointly processed to produce olfactory perception.
Replacing spatial components in activity patterns produce graded perceptual effects that sum linearly. This linearity is not predicted by previously-suggested coding schemes that maximize representational capacity (small changes representing unrelated odors). Temporal features in activity patterns are encoded in sniff-locked time, consistent with previous findings. More surprisingly, we found an additional, stronger component of encoding in the timing of inputs relative to each other, independent of sniff. Both spatial and temporal features are modulated by a preferential weighting of early activity, such that replacing or temporally shifting the earlier-

activated components in the pattern more strongly affects animals' responses, supporting a previously-proposed 'primacy' code in olfaction. All individual effects in the data could be accounted for in a spatio-temporal template matching model.
To our knowledge, this is the first study to map perceptual responses to a broad space of precisely and systematically-manipulated neural activity patterns. Our synthetic approach opens new possibilities in studying olfaction, and provides a novel framework for testing the link between spatio-temporal neural codes and behavior.

Disclosures: E. Chong: None. **M. Moroni:** None. **C. Wilson:** None. **S. Shoham:** None. **S. Panzeri:** None. **D. Rinberg:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.05

Topic: D.05. Olfaction and Taste

Support: NYIT startup funds

Title: Odor identification in the presence of novel background odors: Olfactory captchas

Authors: Y. LI, T. SHE, A. RAHMAN, D. MOGEL, J. WU, A. AHMED, ***G. OTAZU ALDANA**;
NYIT-COM, Old Westbury, NY

Abstract: The visual and auditory systems can identify targets of interest while being immersed in novel and complex environments. The olfactory system can also identify odors of interest in complex natural scenes. Once an animal learns to recognize an odor in a given olfactory environment, it would be advantageous to generalize and recognize the target in multiple different scenes with novel background odors. Recent studies have shown that mice can be trained to recognize odors in the presence of combinations of previously exposed backgrounds odors and it has been proposed that a linear classifier that take as input olfactory receptor activation matches animal's performance. However, we do not know if animals are able to immediately recognize a known target in the presence of novel background odors, nor what algorithm the animals used to solve this task. In order to test the generalization capabilities of mice we used an "olfactory captcha" task. We trained 9 head-fixed animals to perform a go/no-go task using a training set. Mice reached 90% performance after 8-10 days of training. We then tested the detection capability using a test set that included novel background odors that animals have never experienced before, similar to captcha used to distinguish humans from computers. Mice sniff rate increased when they were presented with the novel background odor indicating that the novel background was perceived as a novel odor. Mice correctly identified the target

odors within the novel background odors. Intriguingly, mice required an extra sniff to respond to the target odor and mice response times were slower in the novel odor environment compared to the responses to the training set, which is consistent to the recruitment of recurrent circuitry to solve the task. In order to determine if animals were using a feedforward algorithm, we used intrinsic optical imaging to record dorsal glomerular activation patterns to these odor combinations (training set) and used those data to create a linear classifier for detecting the target odors. We tested the learned linear classifier with odor mixtures that included a novel background odor (test set) and accuracy varied between 65% and 90% accuracy. However, the linear classifier did not predict the animals performance, whereas a non-linear classifier performance correlated with animal behavior ($r=0.51$, $p=0.03$). Our data indicates that animals are able to immediately generalize to novel odor environments and their performance required extra processing time, consistent with recruitment of recurrent circuitry in the bulb performing a non-linear classifier.

Disclosures: **Y. Li:** None. **T. She:** None. **A. Rahman:** None. **D. Mogel:** None. **J. Wu:** None. **A. Ahmed:** None. **G. Otazu Aldana:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.06

Topic: D.05. Olfaction and Taste

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R01DC011286
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NIH NS099714
NS103517
N66001-17-C-4012

Title: Spatio-temporal dynamics of odor responses in the lateral and dorsal olfactory bub

Authors: *K. L. BAKER[1,2], G. VASAN[1,2], A. GUMASTE[2], V. A. PIERIBONE[1,2], J. V. VERHAGEN[1,2];
[1]John B Pierce Lab., New Haven, CT; [2]Yale Univ., New Haven, CT

Abstract: The mammalian olfactory bulb (OB) plays an essential role in odor processing during the perception of smell. Optical imaging of the olfactory bulb has proven to be a key tool in elucidating the spatial odor mapping and temporal dynamics that underlie higher order odor processing. Much is known about the activation of olfactory sensory neuron (OSN) glomerular responses in the dorsal OB (dOB) during odor presentation. However, the dOB provides access

to only ~25% of all glomeruli and little is known about how the lateral OB (lOB) functions during this critical process. Here, we report, for the first time, simultaneous measurements of OSN glomerular activity from both the dOB and lOB in anesthetized OMP-GCamP6 mice, thus describing odor specific spatial mapping and the temporal dynamics of olfactory input to both the dOB and lOB. Odor responses in the lOB tended to be most prominent in the dorso-lateral region. Lateral glomeruli became active (measured by T90) in a roughly dorso-ventral sequence upon odor inhalation, unlike the posterior-anterior activity wave typical of the dorsal glomeruli. Nonetheless, glomerular dynamics reliably differed between odors in the dOB and lOB, as shown before for the dOB. Across the entire dorso-lateral OB the spatial organization of these dynamics could neither be explained by the purely mechanosensitive dynamics (to breathing clean air), nor by the response amplitudes across glomeruli. Instead, these dynamics can be explained by a combination of zonal receptor distributions, associated OB projections and air flow paths across the epithelium upon inhalation.

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Nanosymposium

635. Mapping Chemosensory Representations

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Topic: D.05. Olfaction and Taste

Support: PhD grant for normalien (CDSN, public grant from the ENS), CNRS, INSERM, Lyon 1 University

Title: The change of the hedonic value of an odorant can be read from olfactory bulb activation patterns

Authors: *M. BRETON[1], F. KERMEN[3], N. MANDAIRON[1], A. DIDIER[2];
[2]Biosci., [1]Ctr. De Recherches En Neurosciences De Lyon (CRNL), Bron, France; [3]Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: All odorants have an innate hedonic value. However, previous associations of odorants with food, fear or reproduction influence odor perception and odor-guided behavior. Positive and negative associations thus shape the hedonic value of an odorant and this experience-dependent plasticity of the odor percept is of primary importance for adaptive behavior and animal survival. Since, the olfactory bulb (OB) is involved in coding spontaneous hedonic value and in associative olfactory memory, we asked whether an experience-induced switch in hedonic value would be encoded in the OB. To do this, we caused mice to assign a new positive or negative value to an odorant through appetitive or aversive olfactory learning. The

change of hedonic value can be a strengthening of the spontaneous hedonic value (a spontaneously pleasant odorant associated with a positive value or a spontaneously unpleasant odorant associated with a negative value) or a switch of the spontaneous hedonic value (a spontaneously pleasant odorant associated with a negative value or a spontaneously unpleasant odorant associated with a positive value). The OB responsiveness to odorants in each condition was assessed using Zif268 cell mapping in the granule cell layer. We found a higher activation of the anterior OB after positive reinforcement compared to a negative one. Interestingly, we revealed that the activity in the posterior OB was significantly reduced when the change in hedonic value is switched compared to a strengthening. To further investigate how the antero-posterior modulation of the OB activity is regulated, we analyzed the noradrenergic projections to the OB since the noradrenergic system is involved in olfactory learning. We found a decrease of the density of NET-positive fibers in the posterior OB after a switch compared to a strengthening of the odor hedonic value, regardless of its positive or negative valence. These results indicate a possible role of the posterior OB in coding the congruence between the innate and learned hedonic value under noradrenergic control.

Disclosures: **M. Breton:** None. **F. Kermen:** None. **N. Mandairon:** None. **A. Didier:** None.

Nanosymposium

635. Mapping Chemosensory Representations

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Topic: D.05. Olfaction and Taste

Support: Wellcome Trust Investigator Award (110174/Z/15/Z)
The Francis Crick Institute (FC001153)
Medical Research Council (MC UP 1202/5)

Title: Encoding odour temporal dynamics in the mouse olfactory bulb

Authors: *D. DASGUPTA[1], T. WARNER[1], T. ACKELS[2], A. ERSKINE[1], A. C. MARIN[1], A. T. SCHAEFER[1];
[2]Neurophysiol. of Behaviour Lab., [1]The Francis Crick Inst., London, United Kingdom

Abstract: Turbulent airflow imposes strong intensity fluctuations onto natural odour plumes. It has been hypothesised that such fluctuations could carry information about odour source composition or distance. We have recently shown that mice can indeed extract information from odour concentration fluctuations of a bandwidth up to at least 40 Hz (Erskine et al., 2019). However, it is largely unknown how neurons in the olfactory system can encode temporal features of the odour stimulus.
To understand how neurons in the mice olfactory bulb encode for temporal features we

performed *in-vivo* patch clamp recordings (n = 35 neurons, 62 cell-odour pair, 25 mice) while administering precisely controlled temporally fluctuating odours at 2 Hz and 20Hz. We observed that despite the heterogeneous activity profiles a substantial fraction of OB neurons demonstrated frequency coupling in their sub-threshold domain for 2 Hz (18/62) and 20Hz (10/62) odour stimulus. Furthermore, frequency coupling was largely independent of odour quality. Upon administering odour mixtures, we observed that neurons that coupled well to the mixtures coupled well to at least one of the individual component of the mixture (20/35 cells for 2 Hz case and 14/35 for 20 Hz case). Next, we examined if the correlation structure of composite odours (correlated vs anticorrelated mixing) was encoded differently in these neurons. Indeed, 8/35 neurons in the 2Hz case while 1/35 in the 20Hz case can encode these fine temporal distinction in odour stimulus significantly ($P < 0.05$) in the sub-threshold regime.
Overall, we conclude that projection neurons in the mouse olfactory bulb can encode aspects of the temporal structure of the odour stimulus. Furthermore, our results show evidence of a subset of these neurons that can distinctly demonstrate subthreshold level discrimination in correlated vs. anticorrelated odour stimulus.

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Nanosymposium

635. Mapping Chemosensory Representations

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Topic: D.05. Olfaction and Taste

Support: Canadian Institutes of Health Research (CIHR) (MOP 496401)
Natural Sciences and Engineering Council of Canada (NSERC) (MOP 491009)
NSERC postgraduate scholarships-Doctoral Program (Appl ID: PGSD2- 519452 - 2018)

Title: Olfactory memory representations are stored in the anterior olfactory nucleus

Authors: *A. AQRABAWI[1,3], J. KIM[2,1];
[1]Cell and Syst. Biol., [2]Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]The Picower Inst. for Learning and Memory, MIT, Boston, MA

Abstract: The anterior olfactory nucleus (AON) is the initial recipient of odour information from the olfactory bulb, and the target of dense innervation conveying spatiotemporal cues from the hippocampus. We hypothesized that the AON detects the coincidence of these inputs, generating patterns of activity reflective of episodic odour engrams. Using activity-dependent tagging combined with neural manipulation techniques, we reveal that odour-specific engrams

are stored within the AON and that their activity is necessary and sufficient for the behavioural expression of odour memory. Our findings offer a new model for studying the mechanisms underlying memory representations.

Disclosures: A. Aqrabawi: None. **J. Kim:** None.

Nanosymposium

635. Mapping Chemosensory Representations

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Presentation Number: 635.10

Topic: D.05. Olfaction and Taste

Support: NIDCD Grant 1R01 DC014487-01A1
BBRF 2014 Young Inverstigator Grant

Title: Functional long-range specificity of parallel processing loops in the early mammalian olfaction

Authors: *H. CHAE[1], A. BANERJEE[1,2,3], D. F. ALBEANU[1,2];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Watson Sch. for Biol. Sci., Cold Spring Harbor, NY; [3]New York Univ. Med. Ctr., New York, NY

Abstract: Understanding the interplay between feedforward and feedback neuronal signals across interconnected brain areas is essential for unveiling the computations they perform. Across the brain, specialized long-range circuits support different processing streams. These broadcast information ranging from multiple features of sensory stimuli, decision variables, and inner states to substrates for planning and execution of motor actions. To date, the logic of information flow within the early mammalian olfactory system remains poorly understood. It is not known whether different projection neurons carry different signals to particular areas, and to what degree the feedback from different target brain areas to the sensory periphery is specific to the input channels. Here we find that the two classes of olfactory bulb outputs, the mitral and tufted cells which innervate distinct sets of higher brain areas (including piriform cortex, PC, versus anterior olfactory nucleus, AON), are in turn specifically regulated by differential negative feedback from these areas. These feedback signals were highly precise, acting in an odor-cell pair specific manner, proportionally to the strength of feedforward drive. Overall, bulbar feedback inputs from PC versus AON complemented each other in controlling the response amplitude, timing and pairwise correlation of odor representations at the level of mitral versus tufted cell ensembles. Furthermore, we find that robust and odor specific sensory representations emerge already in the bulb outputs, and are distinct across the mitral and tufted cell populations. Tufted ensembles substantially outperformed mitral cells in decoding concentration invariant stimulus identity, while operating largely in a feedforward fashion. In

contrast, the odor decoding performance of mitral cells was further substantially impaired by the removal of piriform cortex feedback. These results identify two parallel feedforward-feedback loops in the early olfactory system, and indicate they have specialized roles in odor processing. We're currently modulating feedback input to the bulb from the APC and AON respectively in mice engaged in concentration invariant odor discrimination and contextual learning tasks to further probe the roles of cortical feedback.

Disclosures: H. Chae: None. **A. Banerjee:** None. **D.F. Albeanu:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.11

Topic: D.05. Olfaction and Taste

Support: NHMRC Project Grant 1050832 and 1128320

Title: NMDA receptor-dependent dendritic excitability in the piriform cortex *in vivo*

Authors: *M. L. TANTIRIGAMA[1,2,3], J. M. BEKKERS[1];
[1]John Curtin Sch. of Med. Res., The Australian Natl. Univ., Acton, Australia; [2]NeuroCure Cluster of Excellence, Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Fac. of Biol., Humboldt Univ., Berlin, Germany

Abstract: The piriform cortex (PC) is the first cortical destination of odor information. The PC receives afferent olfactory bulb input exclusively in layer 1a onto the distal dendrites of principal cells, which have their somas anatomically segregated in layers 2 and 3. Integration of synaptic inputs in the dendrites is the first stage of cortical odor processing. However, previous work has focused on the output at the somas, and the dynamics of the activity in the dendrites has been directly addressed in only two *in vitro* studies. To address this issue, we sparsely labelled dendrites in the anterior PC with the calcium sensor GCaMP6f and imaged dendritic activity using *in vivo* 2-photon microscopy. We found that all sibling branches of distal dendrites of principal cells exhibited large synchronized calcium transients spontaneously *in vivo*. Somatic application of tetrodotoxin blocked this dendritic activity, confirming that the response was mediated by back-propagating action potentials (bAPs) initiated at the soma. Evoking bAPs by puffing AMPA at the soma also reliably evoked synchronized dendritic calcium transients. However, doing so in the presence of the NMDA channel blocker APV or after removing bulbar input in bulbectomized mice lead to passive conduction of bAPs and an absence of calcium transients in distal dendrites. Our results suggest that the ongoing excitation provided by spontaneous bulbar activity (which is absent *in vitro*) enables bAP-evoked dendritic calcium

spikes to occur *in vivo*. We speculate that dendritic calcium spikes are required for olfactory coding and learning.

Disclosures: M.L. Tantirigama: None. **J.M. Bekkers:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.12

Topic: D.05. Olfaction and Taste

Support: Kavli Institute for Brain and Mind, UCSD
NIH

Title: Winner-take-all motifs strike a balance between discrimination and learning

Authors: *S. SRINIVASAN[1], S. NAVLAKHA[2];
[1]Salk Inst. and KIBM, UCSD, La Jolla, CA; [2]The Salk Inst., La Jolla, CA

Abstract: The mammalian piriform cortex and insect mushroom body (MB) are required for odor discrimination and learning. Studies have shown that despite inter-trial variability, animals learn to discriminate even closely related odors. What are the mechanisms that enable animals to learn to discriminate despite variability? To answer this question, we used a quantitative model of MB, and calcium imaging data. In MB, odors activate a distributed neuronal ensemble. The ensemble activity is sparsened by a winner-take-all motif, wherein negative feedback between MB cells and an inhibitory anterior paired lateral (APL) neuron suppresses all but the most frequently responsive cells. Our examination of this circuit suggests two mechanisms by which MB manages learning and discrimination despite variability. First, APL inhibition is linear, ensuring that MB activity remains sparse at 5-15 %, aiding discrimination. Second, although feedback inhibition increases variability and reduces learning efficiency, variability is beneficial as even highly similar odors differ. Thus, while APL reduces learning efficiency, it also provides mechanisms for distinguishing coarse and fine-grained differences in stimuli. These properties might apply to the piriform cortex, which shares many of the same features, and even other circuits with winner-take-all motifs like the hippocampus.

Disclosures: S. Srinivasan: None. **S. Navlakha:** None.

Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.13

Topic: D.05. Olfaction and Taste

Support: Doctoral fellowship - French Ministry of Research and Education

Title: The reward system supports spontaneous attraction to odorants

Authors: *L. CHALENÇON[1], M. MIDROIT[2], M. BRETON[1], M. THEVENET[1], J. SACQUET[1], N. NOURY[3], J. FOREST[1], M. RICHARD[1], A. MILTON[4], A. FOURNEL[1], C. FERDENZI[1], D. W. WESSON[5], A. DIDIER[1], M. BENSAFI[1], N. MANDAIRON[1];
[1]CRNL, Lyon, France; [2]Univ. de Genèvre, Genève, Switzerland; [3]INL, Villeurbanne, France; [4]Cleveland, Cleveland, OH; [5]Pharmacol. & Therapeut., UNIVERSITY OF FLORIDA, Gainesville, FL

Abstract: Hedonic tone is the most salient perceptual features of odors. Indeed, some odorants trigger behavioral attraction that is essential for animal survival. A neural signature of positive odor hedonic is present in the olfactory bulb, the first cortical relay of the olfactory information. However, the neural underpinning allowing converting this hedonic representation into approach behaviors is unclear. We test here the hypothesis that the reward system is involved in driving spontaneous attraction to odorants and that thus odorants by themselves can act as reinforcing stimulus.
Using psychophysics and video tracking in humans, we found that an odorant that is rated as much liked is also very wanted. This motivational aspect of odor perception is also demonstrated by a higher speed of approach to the odor source, a slower speed of withdrawal, and a shorter distance kept from the odor source in respond to pleasant compared to unpleasant odorants. To confirm this motivational response to pleasant odorants, we then used a standardized protocol called conditioned place preference in a living lab. This test is widely used to assess whether a stimulus can serve as a reinforcer and solicits the reward system as do the drugs of abuse or natural reinforcers in rodents and more recently in humans. This second set of studies revealed that an attractive odorant is able to induce place preference in humans. We plan to complete these data by the analysis of fMRI activity of the reward system in response to attractive odorants. To further investigate the brain mechanisms of odor attraction at a cellular level, we completed these data by combining different technics in mice including fine imagery of cellular activation, recording of neural responses and neural activity modulation using optogenetics in freely moving mice. Using immediate early gene mapping, we found that among the secondary olfactory structures, only the olfactory tubercle that is part of the ventral striatum, preferentially responds to attractive odorants. This was confirmed by multiunit recording. We investigated the other main structures of the reward system and found that they were differentially recruited based on odor hedonic value. Odor-driven place preference learning, dependent on dopamine transmission, and self-stimulation mediated by the olfactory bulb in mice further indicated the functional implication of the reward system in coding odor attractiveness. All together, these data support the view that unlearned pleasant odorants can be rewarding.

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Nanosymposium

635. Mapping Chemosensory Representations

Location: Room S106

Time: Wednesday, October 23, 2019, 8:00 AM - 11:30 AM

Presentation Number: 635.14

Topic: D.05. Olfaction and Taste

Title: Visualized odor encounters show how navigation is driven by whiff timing

Authors: *M. DEMIR[1], N. KADAKIA[1], D. A. CLARK[1,2,3], T. EMONET[1,2,3];
[1]Molecular, Cellular, and Developmental Biol., [2]Interdepartmental Neurosci. Program, [3]Dept. of Physics, Yale Univ., New Haven, CT

Abstract: To find food, mates, and egg-laying sites, insects navigate complex odor plumes shaped by turbulent air flows which erase any standing gradients. In such environments, odor whiffs arrive intermittently and their intensities and durations vary rapidly over orders of magnitude. However, how insects navigate such intermittent odor plumes remains unclear due to the technical challenges in measuring odorants on unrestrained behaving insects. Here we introduce a novel wind tunnel-based walking assay for fruit flies, *Drosophila melanogaster*, which along with our recent discovery of a visible attractive odor (smoke), allows us to quantify the stimulus and the fly behavior simultaneously. Our results show that in distinct odor environments flies exhibit drastic changes in their turning and stop-walk behaviors. Flies make more frequent turns and stop-walk transitions in intermittent plumes than straight plumes. Upon sequential plume encounters flies bias their orientations upwind, and this upwind bias is correlated with whiffs counts, strikingly not with duration of the odor exposure. Separate decision algorithms are executed during walks and stops. While walking, probability to stop is diminished with each individual whiff, not with integrated whiff counts. Conversely, when stopped, probability to walk is boosted with whiff counts integrated during the stop, not with individual whiffs. Stochastic models implementing these algorithms adequately recapitulated statistical properties of the data. These results present that insects use timing of odor encounters, and accumulated olfactory evidence to modulate their locomotion while navigating intermittent odor plumes. Taken together, this work provides an important step in elucidating the logic behind the insect olfactory navigation, which is essential for insect survival.

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Nanosymposium

636. Sex Differences in Response to Stress

Location: Room N427

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Presentation Number: 636.01

Topic: F.04. Stress and the Brain

Support: NIDA T32 Training Grant 5T32DA007237-28
NSF IOS-1552416

Title: And the hits just keep on coming: Sex-specific effects of multiple stressor exposures on cognition

Authors: *S. ECK[1], C. ARDEKANI[1], D. LEE[1], M. SALVATORE[1], A. HALL[1], S. FAMULARO[1], D. A. BANGASSER[2];
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Abstract: The experience of early life stress increases risk for a variety of psychiatric disorders, including depression, anxiety disorders, and substance use disorder, all of which share cognitive impairments as a common feature. In order to study how these cognitive risks develop, we utilized a rodent model of early life stress called the limited bedding and nesting model (LBN), which mimics the low resource environment that characterizes poverty and induces stress in pups via disrupting maternal care behaviors (Ivy et al. 2008). Analysis revealed that LBN dams engaged in more pup-directed behaviors (e.g., nursing) and less self-care behaviors (e.g. resting outside of the nest) than control dams, suggesting a behavioral compensation for the lack of resources. This compensation is not sufficient to prevent detrimental outcomes from this model, however. For example, LBN rats show slower body weight gain compared to sex-matched controls. One aspect of cognition that is impaired by stress is memory. To test whether LBN impairs this type of cognition we employed the novel object recognition (NOR) task, which is known to be sensitive to stress modulation. Like others, we find that LBN alone does not disrupt the simple cognitive task of NOR in males or females. However, in humans, individuals who experience early life stress are more likely to experience additional stressors in adulthood. To model this in rodents, we developed a novel two-hit model of stress in which LBN pups are also exposed to a 6-day chronic variable stress procedure once they reach adulthood. Interestingly, while neither LBN nor adult stress alone impair NOR performance in males or females, male rats that are exposed to both LBN and adult stress do show impaired performance compared to controls. Ongoing studies are also exploring the effect of LBN on cognitive flexibility across development and we predict males will be more affected. Together, these findings indicate that LBN may predispose males, but not females, to be more susceptible to the effects of subsequent stressors on cognition.

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Nanosymposium

636. Sex Differences in Response to Stress

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Time: Wednesday, October 23, 2019, 8:00 AM - 11:15 AM

Presentation Number: 636.02

Topic: F.04. Stress and the Brain

Support: NIMH R01 (MH111604)
MSU DCF Fellowship

Title: Sex differences in hippocampal afferent excitability underlie anhedonia following stress

Authors: *C. MANNING[1], E. S. WILLIAMS[2], H. LYNCH[2], N. DUNQUE-WILKENS[2], A. EAGLE[2], A. B. SWIFT-GALLANT[5], S. CHINNUSAMY[3], G. M. LEINNINGER[3], C. L. JORDAN[1], A. ROBISON[4];
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Abstract: Women are twice as likely as men to be diagnosed with a mood disorder, but the neurophysiological contributions to this disparity are unclear. The ventral hippocampus (vHPC) integrates signals encoding stress, learning and memory, and motivated behaviors, and increased activity of glutamatergic projections from vHPC to nucleus accumbens (NAc) drives maladaptive motivated behaviors following social stress. However, the role of this circuit in sex differences in response to stress has not been studied. Here, we reaffirm that females, but not males, show anhedonic behavior after subchronic variable stress, concordant with a novel finding of increased excitability of female vHPC-NAc neurons. We also show that this sex difference in behavior and physiology is dependent on adult gonadal testosterone, as orchidectomy of males causes vulnerability to stress-induced anhedonia, while testosterone replacement in ovariectomized females prevents the anhedonic effect. This sex difference in behavior is driven by the activity of these neurons, as DREADD-mediated increased activity of vHPC-NAc neurons drives susceptibility in males, while decreasing activity of this circuit induces stress resilience in females. Taken together, our data suggest that hormone status of adult mice drives sex differences in stress-induced anhedonia in part through controlling activity of the vHPC-NAc circuit. This discovery may in part explain the clinical observation that women are more than twice as likely as men to experience depressive disorders, paving the way for sex-specific, circuit-based treatment of depression.

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Nanosymposium

636. Sex Differences in Response to Stress

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Presentation Number: 636.03

Topic: F.04. Stress and the Brain

Support: IKY-DAAD 2015

Title: Sex and age differences in hippocampal metabolism following aromatase inhibition and forced swim test

Authors: *N. KOKRAS[1,2], M. KORONAIOU[1], T. D. CHARLIER[3], S. P. CARO[4], C. TURCK[5], M. FILIOU[6], C. DALLA[1];
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Abstract: Aromatase inhibitors block the conversion of androgens to estrogens and are indicated for the treatment of breast cancer in postmenopausal women, but they are increasingly used “off-label” in premenopausal women for breast cancer and infertility treatment. In addition, aromatase inhibitors are suspected of psychotropic effects due to inhibited estrogen production in the brain. We have recently shown that subacute, but not chronic, treatment with the aromatase inhibitor letrozole produces an antidepressant effect in young female rats and sustained aromatase inhibition results in neurotransmitter level changes in male and female brains. In this study we explore the effects of subacute letrozole treatment in young cycling females and aged female rats in senescence in comparison to young and aged males. Adult and aged male and adult cycling and aged female rats in senescence were used in this study. All rats received a subacute letrozole treatment consisting of 3 injections in 24 hours. Estrous cycle and senescence were estimated in young and aged females respectively through vaginal smears. We evaluated behavioral response in the open field test and the forced swim test. Hormone levels after behavioral testing and tissue brain samples were collected for analysis. To assess the effects of letrozole administration, we compared the metabolite profiles in the hippocampus of letrozole- or vehicle-treated male and female young and aged rats. We used a targeted mass spectrometry-based metabolomics platform measuring up to 300 metabolites. Data were analyzed by MetaboAnalyst. Statistical analysis showed significant sex and age main effects and interactions in the open field and forced swim test. Letrozole treatment induced significant alterations in levels of metabolites in young females. SAM analysis revealed altered levels of 10 metabolites in the hippocampus (FDR<0.05) between letrozole- and vehicle-treated young female rats. The observed metabolite changes were blunted in the hippocampus of older females. These metabolites are involved in betaine and

amino acid metabolism and letrozole treatment reduced their levels. Present findings, in light of our previous studies, show a complex sex- and age- dependent effect of letrozole treatment that possibly results not only in transient behavioral changes, but also in more permanent neurobiological alterations in the brain of rats treated with aromatase inhibitors.

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Nanosymposium

636. Sex Differences in Response to Stress

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Presentation Number: 636.04

Topic: F.04. Stress and the Brain

Support: Hope for Depression Research Foundation

Title: Transcriptional profiling of the stressed hippocampus: Does sex make a difference?

Authors: *J. MARROCCO[1], N. R. EINHORN[1], S. G. CARADONNA[1], C. LE FLOCH[1], A. LIHAGEN[2], G. H. PETTY[3], E. GATTA[4], H. KHALIL[5], E. JAŠAREVIć[6], F. S. LEE[7], B. S. MCEWEN[1];
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Abstract: Whole-genome analysis of discrete cell populations has advanced the dissection of circuits responding to stress, such as the hippocampal subfields. Within the same brain circuits, females and males activate distinct sets of genes in response to similar environmental challenges. We examined the transcriptomic profiling, along with behavioral correlates and neuroanatomical changes, in mice maintained on chronic low-dose (25mg/l) oral corticosterone (CORT), a mouse model that shows disruption of the hypothalamic-pituitary-adrenal axis. This animal model meets the criteria of construct, face, and predictive validity for stress-related psychiatric disorders associated with prolonged exposure to glucocorticoids. Anxiety- and depression-like behaviors, referred to as emotional behavior, were tested with the light-dark box and the splash test, respectively. A z-normalization applied across complementary measures of behavior showed that CORT increased emotional behavioral scores in males but not in females. However, when maintained on chronic oral CORT, both females and males exhibited comparable loss of dendritic complexity and length in the granular neurons of ventral dentate gyrus. We then dissected the ventral hippocampus to study the transcriptional profiling of either sex using RNA-sequencing. Chronic oral CORT triggered unique gene sets in male and female mice.

Furthermore, CORT treatment affected the levels of different exons of the glucocorticoid receptor*Nr3c1*in males versus females. Thus, prolonged exposure to CORT leads to similar neuroanatomical changes in the ventral hippocampus of female and male mice, but there exist sex differences that intersect affective behavior and transcriptional signature. This favors the use of big data to probe dissimilar gene functions that underlie sex-specific endophenotypes in animal models of stress.

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Nanosymposium

636. Sex Differences in Response to Stress

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Presentation Number: 636.05

Topic: F.04. Stress and the Brain

Support: NIH Grant NR014886

Title: Chronic adolescent stress has sex-specific consequences on adult cognitive function

Authors: *M. M. HYER, G. A. SHAW, E. SORIANO, D. MUKHARA, C. SALOME-SANCHEZ, G. N. NEIGH;
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Abstract: Chronic stress can lead to a wide range of health deficits. The stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, undergoes significant refinement during adolescence, thus chronic adolescent stress (CAS) can induce long-lasting, sex-specific changes in HPA function. Downstream effects of altered HPA function include emotional dysregulation and vulnerability to cognitive impairments. Despite these consequences, the extent to which CAS impairs cognition remains unknown. As females are twice as likely as males to suffer the negative consequences of stress, such as depression and post-traumatic stress disorder, it is likely that CAS-induced outcomes are sex-specific. In the current study, male and female Wistar rats remained non-stressed (NS) or were chronically exposed to varied psychosocial stressors during adolescence then underwent cognitive assessment as adults. While memory in adult males and females remained unaltered ($p>0.05$), CAS females showed improved ability to locate a target in the Barnes Maze task compared to NS females ($p<0.05$). However, when the task was reversed and the target was moved to a new location, CAS females performed worse than NS females at learning the new location of the target ($p<0.05$). To determine the extent of this cognitive rigidity, females were trained on a set-shifting task requiring them to learn cue associations and then unlearn them for a new, more favorable association. CAS females again showed no deficits

in learning but were slower than NS females at unlearning an old association in favor of the new, more relevant association ($p<0.05$). Taken together, these findings suggest that while CAS may initially improve spatial learning in females, it impairs cognitive flexibility in adulthood. As hippocampal (HPC)-prefrontal cortex (PFC) circuitry underlies these behaviors, we investigated neural consequences of CAS in females and males. CAS females show greater GluA1 AMPA subunit expression in the HPC compared to NS controls suggesting a mechanism by which learning may be altered. Further investigation of neural mechanisms in the HPC-PFC circuitry is ongoing. As males remained largely unaffected, these findings highlight the importance of sex in the consequences of chronic stress.

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Nanosymposium

636. Sex Differences in Response to Stress

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Presentation Number: 636.06

Topic: F.04. Stress and the Brain

Support: 1K99AG059953-01A1

Title: Early life stress impacts late adulthood anxiety like behavior in a sex specific manner

Authors: *H. C. HUNSBERGER, C. A. DENNY;
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Abstract: Anxiety disorders are the most common mental illness in the United States, affecting 40 million adults every year. Anxiety symptoms in older adults can cause poor cognitive performance, memory and sleeping disturbances, and results in higher risk of somatic illness. In addition, women have consistently higher prevalence rates of anxiety disorders compared to men. How gender affects age of onset, chronicity, and comorbidity is unknown. Furthermore, despite the prevalence of anxiety, the developmental risk factors are not well understood. One potential risk factor for late-life anxiety is early life stress (ELS). In humans, this translates to childhood maltreatment, family problems, death of a family member, poverty, etc. Here, we aimed to determine the impact of ELS on 1) late-life behavior and 2) neuronal activation, in male and female mice.
To study the impact of ELS, we used our activity-dependent tagging system, the ArcCreER^{T2} x channelrhodopsin (ChR2)-EYFP mice. These mice allow for brain-wide indelible labeling of neurons activated during learning, which then can be compared with secondary neuronal ensembles activated during memory retrieval. The neurons activated at both time points represent a memory trace or engram. First, we stressed the mice at 2 months of age in a

contextual fear conditioning paradigm. We then tested anxiety-, depressive-like, and cognitive behavior at 6 months of age. Our results show that stressed male mice exhibit less anxiety-like behavior in late-life compared to stressed females who exhibit greater anxiety-like behavior. A majority of ELS studies use maternal separation as their paradigm to induce stress during the first two postnatal weeks of life. However, we show that you can also induce older adulthood anxiety using acute stress after the critical time window of development. We believe this is also translatable to humans as many traumatic events happen during childhood and teenage years. We are now examining the neuronal differences between male and female mice after exposure to an anxiety-like task by using microscopy and calcium imaging. We will also examine whether this behavior persists across the life-span of the animal. These results will help to determine how ELS impacts the brain in a sex-specific manner.

Disclosures: H.C. Hunsberger: None. **C.A. Denny:** None.

Nanosymposium

636. Sex Differences in Response to Stress

Location: Room N427

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Presentation Number: 636.07

Topic: F.04. Stress and the Brain

Support: NARSAD Young Investigator Award from the Brain & Behavior Research Foundation

Title: Of mice and wo/men: Translating the relationship between cytokines and depression associated behavior

Authors: *J. R. RAINVILLE[1], M. SCHNEIDER[2], F. CATHOMAS[3], J. W. MURROUGH[2], G. E. HODES[1];
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Abstract: Within the brain, the underlying biological mechanisms of depression differ between men and women. Recent work has demonstrated the peripheral immune system influences the brain's response to stress and subsequent behavior. The peripheral immune system is altered in patients with depression and may contribute to sex differences in the prevalence and symptoms of depression. We took an unbiased approach to examine differences in plasma cytokine expression between pre-menopausal women and age-matched men with depression. We modeled these changes in immune activity with mouse stress paradigms to uncover the relationship between peripheral cytokine expression and behavior. We used Multiplex ELISA to quantify plasma expression levels of 29 different cytokines in plasma samples from men and women

diagnosed with depression (treatment resistant vs. non treatment resistant), as well as from mice of both sexes following either social defeat stress or chronic variable stress. Our results show women with treatment resistant depression have greater immune activation than any other group. We were able to model the IL-6 response in females following social defeat stress, and a similar GM-CSF response following 28-days of chronic variable stress in females. All cytokine concentrations were correlated with symptoms reported by patients on the Quick Inventory of Depressive Symptomology (QIDS-SR 16), or with behavior scores from a battery of ethologically relevant depression-like behaviors in mice, including forced swim test, splash test, and novelty suppressed feeding. Cluster analysis shows different associations between groups of cytokines and specific behaviors, both in patients with depression and in two mouse stress models for depression. These results confirm sex-specific immune system activation in depression, and demonstrate the translational potential for using stress paradigms in mice to model specific immune responses.

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Nanosymposium

636. Sex Differences in Response to Stress

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Topic: F.04. Stress and the Brain

Support: NIH Grant R56 MH114193

Title: Interrogating the contribution of CB1 receptor signaling to sex differences in context generalization and the activity of the ventral hippocampus-basolateral amygdala circuit

Authors: *K. A. HUCKLEBERRY, R. SHANSKY;
Behavioral Neurosci., Northeastern Univ., Boston, MA

Abstract: Post-traumatic stress disorder (PTSD) costs the US as much as $2 billion per year, with as many as 10.1% of the US adult population experiencing symptoms at some point within their lifetime. There is a marked gender disparity in PTSD diagnoses, with women comprising at least two-thirds of PTSD patient populations. Because PTSD is characterized by increased generalization of fear to neutral or safe environments and cues, women's increased susceptibility to PTSD could be attributable to sex differences in how contextual information regulates the expression of fear. The hippocampus processes contextual information and provides valence to contexts via the ventral hippocampus's (vHPC) connections to the basolateral amygdala (BLA), an area required for fear conditioning (FC). We predict that generalization of fear reflects a failure of the BLA to integrate contextual information from the vHPC into the fear memory

during conditioning. One novel and under-explored mechanism for regulating activity in this circuit could be via local endocannabinoid (eCB) signaling. Within the hippocampus, the primary eCB receptor, CB1, is localized on the presynaptic terminals of interneurons. Preliminary data from our lab demonstrates that systemic administration of the CB1 receptor antagonist AM251 prior to FC resulted in increased context fear generalization in females but not in males. These data suggest that sex differences in fear generalization may be attributable to differences in how the CB1 receptor mediates activity within the vHPC-BLA circuit. We hypothesize that, in females, CB1 receptor blockade prevents disinhibition within the hippocampus, thereby decreasing activity in glutamatergic projection neurons and thus ultimately blocking transmission of contextual information to the BLA. Without this information, the BLA is unable to integrate contextual information into the fear memory, thereby increasing the generalization of context-induced fear. To test this, we used an intersectional trans-synaptic viral strategy to label the BLA targets of vHPC projections in male and female rats. We then fear conditioned the rats and examined the activity of BLA neurons in response to exposure to an alternate context. Due to our preliminary data suggesting a sex-dependent role for the CB1 receptor in context generalization, we predict that AM251-treated females will exhibit less activation in *labeled* BLA neurons and more activation in *unlabeled* BLA neurons.

Disclosures: K.A. Huckleberry: None. **R. Shansky:** None.

Nanosymposium

636. Sex Differences in Response to Stress

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Presentation Number: 636.09

Topic: F.04. Stress and the Brain

Title: Sex differences in effects of treatment with oxytocin or selective serotonin reuptake inhibitor on behavioral phenotype and receptor expression in socially defeated prairie voles

Authors: L. H. HALE, ***M. C. TICKERHOOF**, A. S. SMITH;
Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS

Abstract: Social anxiety disorder is a prevalent mental illness that significantly impacts the social lives of both men and women, but current treatment approaches using selective serotonin reuptake inhibitors (SSRIs) have limited success. Oxytocin has recently risen as an attractive candidate for treatment of social anxiety due to its role in social behavior in both humans and animal models, but its effectiveness in models of social anxiety disorder is not well characterized. Social defeat stress is an animal model of social conflict that reliably induces a social avoidance phenotype, reflecting the primary symptom observed in humans suffering from social anxiety disorder. However, modeling of social defeat stress has been largely limited to males, primarily due to difficulty in developing ethologically relevant models of female-directed

aggression in rodents. Here, we used the socially monogamous prairie vole, which exhibits aggressive behavior in both sexes after the formation of a pair bond, to examine the effects of oxytocin and SSRI treatment following social defeat stress in both males and females. A time course study of the effects of social defeat on social behavior revealed a social avoidance phenotype as soon as one day after defeat in both sexes, and this phenotype persists at least eight weeks after social defeat stress. Oxytocin receptor (OTR) in multiple mesocorticolimbic and paralimbic regions was downregulated in defeated females starting one week after defeat and persisting to the eighth week after defeat. In males, 5-HT_{1A} expression decreased in the basolateral amygdala and dorsal raphe nucleus starting at one week and four weeks post-defeat, respectively. Defeated males also exhibited a transient increase in 5-HT_{1A} expression in the ventral tegmental area; this normalized by week four post-defeat. Intranasal treatment with oxytocin had a negative effect on sociability in non-defeated animals in both sexes. This decrease in sociability correlated with a decrease of OTR in the nucleus accumbens core and basolateral amygdala of females. In defeated prairie voles, intranasal oxytocin reversed the social avoidance phenotype in females, but not males. This behavioral effect corresponded with a normalization of OTR levels in the nucleus accumbens and basolateral amygdala of defeated females. Interestingly, there was no effect of SSRI treatment on sociality or receptor expression in voles of either sex. These results implicate a potential sex-specific and stress context-dependent role of OTR in mesolimbic regions in changes in social behaviors.

Disclosures: L.H. Hale: None. **M.C. Tickerhoof:** None. **A.S. Smith:** None.

Nanosymposium

636. Sex Differences in Response to Stress

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Topic: F.04. Stress and the Brain

Support: R000 DA033372

Title: Adolescent isolation stress shows sex specific alterations in glutamatergic signaling in the nucleus accumbens

Authors: *A. U. DEUTSCHMANN, L. A. BRIAND;
Psychology, Temple Univ., Philadelphia, PA

Abstract: Adolescence is a critical period in brain development and stressful events during this time can have tremendous effects on the maturating brain. Specifically, adolescent social stress puts individuals at increased risk for multiple psychiatric diseases including substance use disorders. The nucleus accumbens plays a key role in motivation and addictive behavior. However, little is known about how adolescent social stress alters synaptic plasticity in the

accumbens and its specific afferent projections. The current studies utilized an adolescent isolation stress model that elicits an increase motivation for cocaine in adulthood to examine the effects of stress on accumbal physiology in both male and female mice. As sex differences exist in multiple psychiatric disorders influenced by stress, we were interested in the interaction between adolescent stress and sex on accumbal physiology. sEPSCs recordings show a significant increase in frequency in males and females which indicates changes on the presynaptic side of the medium spiny neuron synapse. This was further supported by electrically evoked paired-pulse ratio (PPR) recordings showing an overall decrease in paired-pulse facilitation in the nucleus accumbens core. These results indicate that adolescent social stress affects presynaptic short-term plasticity. The nucleus accumbens core is innervated by afferents from several brain regions including the prefrontal cortex (PFC), the ventral hippocampus (vHIPP), and the basolateral amygdala (BLA). Using an *ex vivo* optogenetic approach, we found that stimulating projections from the vHIPP recapitulated the PPR effects of electrical stimulation in both males and females. In contrast, stimulating the projection from the PFC revealed an effect of adolescent isolation only in female mice. Taken together our data revealed sex-specific alterations in glutamatergic presynaptic plasticity in the nucleus accumbens core in adult mice following adolescent social isolation stress.

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Nanosymposium

636. Sex Differences in Response to Stress

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Presentation Number: 636.11

Topic: F.04. Stress and the Brain

Support: Canadian Institute of Health Research (MOP 142308)

Title: Beyond sex differences: Ovarian hormones as determinants of risk and resilience in females

Authors: *R. S. EID, S. E. LIEBLICH, P. DUARTE-GUTERMAN, S. J. WONG, J. A. CHAITON, L. A. M. GALEA;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The prevalence of depression is two-fold higher in women than in men, yet little attention is paid to female-specific factors than can contribute to risk or resilience. Ovarian hormones influence the outcomes of stress exposure and are implicated in depression, however their roles are often complex and contradictory. Importantly, ovarian hormones have potent neuroplastic effects and immunomodulatory properties, which may underlie their roles in stress and depression. Using sub-chronic and chronic stress paradigms in female rodents, we

investigated ovarian hormones at the intersection of stress, neuroplasticity, and neuroinflammation in the hippocampus and frontal cortex. We show that short-term ovariectomy increases depressive-like behaviour under non-stress conditions, and long-term ovariectomy increases susceptibility to the depressive-like outcomes of chronic stress exposure. We then used pharmacological approaches to dissect the contribution of estrogen receptor (ER) subtypes. Selective chronic activation of ER α or β reversed the depressogenic effects of ovarian hormone deprivation under non-stress conditions, but potentiated the depressive-like outcomes of chronic stress exposure. Further, the neuroplastic and neuroinflammatory consequences of stress exposure were dependent on ovarian status with distinct modulatory roles of ER α and β. Finally, we found that ovarian hormones interacted with stress exposure to affect intracellular signaling pathways in the frontal cortex. Collectively, our findings indicate that ovarian hormones influence the neuropathology of stress and should be considered as female-specific determinants of risk and resilience.

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Nanosymposium

636. Sex Differences in Response to Stress

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Topic: F.04. Stress and the Brain

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Title: Altered photoperiod exposure during gestation and early life induces psychiatry-relevant behaviors that are sex-specific

Authors: *M. A. KWIATKOWSKI[1], Z. A. COPE[3], C. J. A. VAN DE CAPPELLE[5], J. DESLAURIERS[4], D. DULCIS[1], J. W. YOUNG[2];
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Abstract: BACKGROUND: A higher incidence of psychiatric diagnoses is reported in people born in late winter/early spring. Mechanisms underlying gestational effects of altered photoperiod exposure in offspring remain unclear. Reducing active (short-active; SA) periods in adult rodents induces depression-like behavior and elevates plasma corticosterone (CORT) in male adult rats. Gestational exposure to SA photoperiod affects serotonergic activity, but its effect on psychiatry-relevant behaviors remains to be determined. We tested whether SA

photoperiod exposure induces the same CORT response in adult female mice and investigated behavioral effects of gestational/early life SA photoperiod exposure in male and female offspring.
METHODS: Female C57BL/6J mice were exposed to normal-active (NA; 12:12 L:D) or SA (19:5 L:D) photoperiod for 14 days, after which tail blood was collected for baseline plasma corticosterone (CORT) assessment. On day 15, tail blood was collected after a 2-hour acute restraint stress vs. single housing (control). Blood samples were analyzed for plasma CORT via ELISA. For gestational experiments, dams and sires were paired for 2 weeks in either NA or SA photoperiod. Resultant pups were maintained in these conditions until weaning (P28), then placed into NA photoperiod until behavioral testing at 10-11 weeks old. Sensorimotor gating (prepulse inhibition; PPI), motivation to obtain reward (progressive ratio breakpoint task; PRBT), risk averse behavior (elevated-plus maze; EPM), and executive function (probabilistic reversal learning task; PRLT) were assessed.
RESULTS: SA-exposed females exhibited higher acute stress/baseline CORT ratios compared to NA-exposed females ($F_{1,19}$=7.3, p=0.01). Gestational/early life SA exposure induced sex-specific behavioral effects in offspring. SA-born males exhibited impaired PPI (sex x photoperiod interaction: $F_{1,230}$=9.8, p<0.01) and reduced motivation to obtain reward in the PRBT ($F_{1,230}$=5.9, p<0.05) vs. NA-born males. SA-born females exhibited risk averse behavior in the EPM (sex x photoperiod interaction: $F_{1,112}$=6.0, p<0.05) and impaired executive function in the PRLT (sex x photoperiod interaction on switches: $F_{1,230}$=3.3, p=0.07).
DISCUSSION: The findings suggest that 1) SA photoperiod alters stress responding and 2) that gestational/early life SA photoperiod exposure induces long-lasting sex-specific effects on psychiatry-relevant behaviors in mice. Future directions include assessing SA-induced CORT response in pregnant dams, as well as assessing SA-induced placental gene expression changes that might contribute to the sex-specific behavioral profiles we observed.

Disclosures: **M.A. Kwiatkowski:** None. **Z.A. Cope:** None. **C.J.A. van de Cappelle:** None. **J. Deslauriers:** None. **D. Dulcis:** None. **J.W. Young:** None.

Nanosymposium

636. Sex Differences in Response to Stress

Location: Room N427

Time: Wednesday, October 23, 2019, 8:00 AM - 11:15 AM

Presentation Number: 636.13

Topic: F.04. Stress and the Brain

Support: HD091376

Title: Insights on generational health consequences of the perceived stress of racism: Maternal preconception stress programs female offspring stress hyper-reactivity

Authors: *Y. M. CISSE[1], S. E. CARTER[2], T. JOVANOVIC[3], T. L. BALE[4];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Georgia State Univ., Atlanta, GA; [3]Emory Univ., Atlanta, GA; [4]Pharmacol., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Despite major advancements in maternal-fetal health, African American women are three times more likely to die in childbirth or postpartum than their non-Hispanic white counterparts, independent of education and income. A known contributing factor, pervasive across socioeconomic status, is the perceived stress of racism (PSR). Racial discrimination experienced across the lifespan promotes a state of chronic stress and allostatic load (AL). PSR is positively correlated with AL, decreased cortisol waking response, and blunted stress responses in African American women. Maternal AL, even prior to pregnancy, is a strong predictor of adverse perinatal outcomes, and offspring neuropsychiatric disease risk. However, little is known about the mechanisms by which pre-conception stress history affects offspring neurodevelopment. We have developed a novel mouse model of maternal preconception stress (MPS), where female, but not male, offspring of MPS dams show elevated adult stress reactivity. Our studies focused on examining changes in neurodevelopment have identified downregulated genes involved in synaptic development and steroid hormone secretion in E12.5 female MPS offspring relative to controls, supporting dysregulation of hypothalamic-pituitary-adrenal (HPA) axis development. As the site of signaling and nutrient exchange, the placenta is a major determinant of fetal growth and developmental outcomes. Placental adaptations modulate the ability of the placenta to support fetal growth in response to an adverse *in utero* environment. To identify mechanisms by which MPS may be altering communication at the maternal:fetal interface, we investigated sex-specific changes in the placental transcriptome. Male placentas of MPS dams had a robust transcriptional response, downregulating genes involved in innate and adaptive immunity and upregulating genes involved in DNA damage response, DNA repair, and mitochondrial translation. However, placentas of female MPS offspring exhibited minimal changes in gene expression. Relative to the cellular stress response in male placentas of MPS dams, the minimal transcriptional response in females suggests impaired placental adaptation that is ultimately detrimental to neurodevelopment. Ongoing studies will address the intergenerational consequences of MPS in female offspring with pre-existing elevated stress reactivity. Together, these studies highlight the importance of female preconception stress experiences on female offspring stress axis programming, a process that may contribute to the generational female-biased racial health disparity.

Disclosures: Y.M. Cisse: None. **T.L. Bale:** None. **S.E. Carter:** None. **T. Jovanovic:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.01

Topic: H.02. Human Cognition and Behavior

Title: How to use transcranial magnetic stimulation to modulate and measure memories in humans?

Authors: *N. S. ROSE, N. YEH, M. WIDHALM;
Univ. of Notre Dame, Notre Dame, IN

Abstract: In this presentation I will review the ways in which my colleagues and I have used transcranial magnetic stimulation (TMS) to modulate and measure memory representations in the human brain. Pairing TMS with simultaneous neuroimaging allows one to ping specific regions of the brain and detect latent memory representations in varying states of activation, analogous to how SONAR emits signal and recovers underlying representations. Our research has used TMS to reactivate and manipulate latent working memories that appeared to have been forgotten (Rose et al., 2016; Widhalm & Rose, 2018). In a related line of research, repetitive TMS protocols have been show to have powerful, lasting effects on episodic memory functioning in healthy and diseased populations. However, our recent systematic review of 59 studies and meta-analysis of 245 effect sizes from 37 articles on healthy younger adults (N=1,061) has revealed complex interactions among several of the many factors that can be manipulated, including stimulation intensity, frequency, timing, and location, as well as experimental design characteristics, such as the type of memory process that is stimulated and the type of memory outcome test that is assessed (Yeh & Rose, submitted). For example, whereas offline 20-Hz rTMS protocols lead to enhancing effects, online 20-Hz rTMS protocols have generally led to negative effects; and there are generally more beneficial effects of 1-Hz rTMS versus other frequencies on episodic memory, especially when applied below- versus at-motor threshold. Although many promising examples are highlighted, the effects of many combinations of parameters remain to be explored in this burgeoning, yet relatively nascent area of research. I highlight many missing gaps for future research to fill, as well as several important design considerations and suggestions to help elucidate the optimal combination of parameters for obtaining the largest beneficial effects of stimulation on memory functioning, which is essential for the development of efficacious translational applications.

Disclosures: **N.S. Rose:** None. **N. Yeh:** None. **M. Widhalm:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.02

Topic: H.02. Human Cognition and Behavior

Support: CNRM-70-3904

Title: Testing cooperation and competition between episodic and procedural memory systems using network-targeted rTMS

Authors: *M. V. FREEDBERG[1], J. A. REEVES[1], J. L. VOSS[2], E. M. WASSERMANN[1]; [1]NIH/NINDS, Bethesda, MD; [2]Med. Social Sci., Northwestern Univ., Chicago, IL

Abstract: Learning skills or habits (procedural learning) relies on the striatum and its interconnected nodes, whereas learning information about facts, objects, and events (declarative learning) relies on a network centered on the hippocampus. These networks are considered to be competitive, such that activation of one system suppresses the other one. Repetitive transcranial magnetic stimulation (rTMS) of the posterior parietal cortex (PPC) can improve declarative memory and enhance resting state functional connectivity (FC) in the hippocampal network, particularly between the hippocampus and the precuneus. We examined FC changes in both networks after PPC rTMS to look for evidence of neural antagonism or competition for brain resources. We delivered daily PPC or vertex rTMS to healthy individuals. rTMS was guided to the PPC subregion maximally connected to the hippocampus. We measured hippocampal and striatal network FC prior to all stimulation and 24 hours after the final rTMS session. In addition to increasing hippocampal network FC, PPC rTMS increased connectedness between the striatum and the rest of the brain. Structural equation modeling revealed significant increases in FC of both the striatum and hippocampus with the precuneus, which is critical for episodic memory retrieval. Data from a subset of participants who underwent PPC rTMS and behavioral testing suggest that PPC stimulation decreases procedural memory along with the expected increase in declarative memory. Additionally, the change in striatum-precuneus FC appears to predict the increase in declarative memory and the decrease procedural memory. Striatum recruitment by the declarative network may be mechanistically related to the declarative memory improvement following PPC rTMS. This may decrease availability of the striatum to the procedural network and affect procedural memory.

Disclosures: M.V. Freedberg: None. **J.A. Reeves:** None. **J.L. Voss:** None. **E.M. Wassermann:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.03

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH113347

Title: Lateral prefrontal goal representations causally influence basolateral amygdala reactivity and behavioral responses to emotional stimuli

Authors: *R. C. LAPATE, M. HECKNER, A. TAMBINI, J. SAKKAS, M. D'ESPOSITO; Univ. of California, Berkeley, Berkeley, CA

Abstract: Contextually flexible representations in lateral prefrontal cortex (LPFC) have been postulated to contribute to cognitive control and goal-oriented behavior. Such context-dependent representations should be especially important for organizing behavior in the face of events that automatically elicit prepotent behavioral responses, such as motivationally-relevant action tendencies typically provoked by emotional stimuli. Here, we tested whether LPFC task goal representations causally modulate emotional processing and promote goal-oriented behavior by combining non-invasive brain stimulation (transcranial magnetic stimulation/TMS) and multimodal imaging (including perfusion arterial spin labeling to index cerebral blood flow (CBF) and fMRI). To identify task goal representations from LPFC and assess the behavioral prepotency of emotional information, participants (n=28, 18-28 y old, 16 females) performed an Affective Go/No-Go (AGNG) task during fMRI scanning. The AGNG task robustly captures approach and avoidance biases provoked by emotional stimuli: positive stimuli typically facilitate “go”, whereas negative stimuli facilitate “no-go” responses. Using a linear classifier, we found that in mid-LPFC, the cross-validated decoding accuracy of task rule (Go/No-Go) in multivoxel activation patterns exceeded chance. Next, we targeted the location of peak multivariate decoding accuracy of task rule within each individual’s LPFC using continuous theta-burst (cTBS), a TMS protocol that has been shown to reduce cortical excitability. We also targeted somatosensory cortex as a control site. Following cTBS, participants performed the AGNG task during scanning. We assessed how altering LPFC goal representations impacted function of the amygdala, a key region involved in the early appraisal of emotional stimuli and in the orchestration of behavioral and physiological responses to them. Following LPFC cTBS, amygdala CBF was reduced. Further, basolateral amygdala reactivity to negative faces (relative to positive ones) was significantly attenuated. Critically, and consistent with the idea that LPFC cTBS inhibited amygdala function, participants’ error rates—specifically, false alarms—in the AGNG task increased in response to negative faces, suggesting a reduction in avoidance behavior during threat processing. Collectively, these results converge to highlight a network-level and valence-specific impact of LPFC-amygdala interactions in supporting cognitive control and shaping emotionally-guided behavior.

Disclosures: R.C. Lapate: None. **M. Heckner:** None. **A. Tambini:** None. **J. Sakkas:** None. **M. D'Esposito:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.04

Topic: H.02. Human Cognition and Behavior

Support: NIMH R01-MH106512
NIMH R01-MH111790
NINDS T32-NS047987

Title: Immediate enhancement of hippocampal memory processing via frequency- and location-targeted TMS-fMRI

Authors: *M. S. HERMILLER, R. A. YOUNG, Y. CHEN, T. B. PARRISH, J. L. VOSS; Northwestern Univ., Chicago, IL

Abstract: Synchronous theta-band (4-8-Hz) activity among hippocampal-cortical network (HCN) regions is thought to support episodic memory. We sought to causally test the relationship between theta and HCN memory processing by assessing the immediate impact of noninvasive transcranial magnetic stimulation (TMS) delivered in a theta-burst (TBS) pattern on hippocampal memory function. During simultaneous TMS/fMRI scanning, subjects (N=16) performed a task that allowed us to measure memory processing (complex scene encoding), relative to a numerical processing control task (odd/even number judgments). For each trial, two seconds of TBS was delivered immediately prior to stimulus (i.e., scene or number) onset. Stimulation was delivered to an HCN-targeted location (left parietal cortex) for half the trials and an out-of-network active-control location (motor cortex) for the other half. To test the relevance of the stimulation frequency pattern, TBS was compared to a beta frequency-control (12.5-Hz). Thus, task-evoked hippocampal activity was contrasted for trials with scenes versus numbers, TBS versus beta, and parietal versus motor sites. This allows us to test the hypothesis that only TBS delivered to the hippocampal network would selectively enhance hippocampal scene encoding, relative to numeric processing, beta-frequency stimulation pattern, and out-of-network stimulation location controls. Indeed, only HCN-targeted TBS significantly improved later recollection of scenes, relative to out-of-network TBS ($P<0.001$) and relative to beta ($P<0.05$). Further, there were significant effects of stimulation frequency and location on downstream hippocampal activation during later-recollected scene processing, such that greater evoked activity was measured for HCN-targeted theta-burst relative to control conditions ($Ps<0.01$). Notably, these effects were specific to the targeted left hippocampus, not the right hippocampus. Thus, HCN-targeted theta-burst was more effective at promoting subsequent recollection and led to greater hippocampal activity evoked by scenes during successful encoding. These findings suggest that TBS can immediately modulate downstream hippocampal memory processing and provide causal evidence to support the role of HCN theta in episodic memory.

Disclosures: M.S. Hermiller: None. **R.A. Young:** None. **Y. Chen:** None. **T.B. Parrish:** None. **J.L. Voss:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.05

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant 378291
NSERC Postgraduate Scholarship

Title: Precuneus stimulation alters the spatiotemporal neural dynamics of autobiographical memory

Authors: *M. HEBSCHER[1], C. IBRAHIM[2], J. A. MELTZER[3], A. GILBOA[3];
[1]Feinberg Sch. of Med., Northwestern Univ., Chicago, IL; [2]Dept. of Pharmacol., Univ. of Toronto, Toronto, ON, Canada; [3]Rotman Res. Inst., Baycrest, Toronto, ON, Canada

Abstract: Autobiographical memories (AMs) involve complex representations of personal events that allow individuals to re-experience past events in detail. A rich body of literature has identified a widespread network of brain regions involved in AM. During retrieval, the hippocampus and surrounding medial temporal lobe (MTL) regions are thought to mediate the coordinated reinstatement of information from neocortical regions. Posterior parietal regions are believed to play a particularly important role in subjective aspects of AM recollection such as vividness and confidence. However, little is known about the complex interactions between regions involved in AM and the dynamics of their recruitment. Furthermore, few studies to date have demonstrated the causal involvement of neocortical regions in AM retrieval. We used inhibitory noninvasive stimulation to determine the causal role of the precuneus in the dynamics of AM retrieval. We applied continuous theta burst stimulation to the precuneus and recorded neural activity during AM retrieval using magnetoencephalography (n = 23). Compared to vertex, precuneus stimulation altered both MTL-neocortical communication as measured by theta-gamma oscillatory coupling, and evoked neural activity. Alterations in both oscillatory and evoked neural activity were associated with subjective measures of AM retrieval. These findings support the hypothesized role of the MTL in mediating cortical reinstatement, and the critical role of the precuneus in subjective AM. This study provides novel insights into the spatiotemporal dynamics of AM retrieval and demonstrates the feasibility of using noninvasive stimulation and electrophysiology to study complex, naturalistic memory functions.

Disclosures: M. Hebscher: None. **C. Ibrahim:** None. **J.A. Meltzer:** None. **A. Gilboa:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.06

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant U01 AG050618

Title: Site-, timing-, and load-specific effects of online repetitive transcranial magnetic stimulation (RTMS) on working memory (WM)

Authors: *L. BEYNEL[1], S. W. DAVIS[1], C. A. CROWELL[1], S. A. HILBIG[1], H. PALMER[1], A. BRITO[1], C. HILE[1], W. LIM[1], D. NGUYEN[1], M. DANNHAUER[1], A. V. PETERCHEV[1], R. CABEZA[1], S. H. LISANBY[2], B. LUBER[2], L. G. APPELBAUM[1];
[1]Duke Univ., Durham, NC; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Working memory (WM) is a critical cognitive function that relies heavily on the fronto-parietal (FP) cortical network and is widely affected with aging. In the current studies, we tested the capacity to enhance WM in a group of young and elderly healthy participants through application of repetitive transcranial magnetic stimulation (rTMS). Two similar 6-day studies were conducted applying rTMS over the left dorsolateral prefrontal cortex (l-DLPFC, study 1), or the left parietal cortex (l-PC, study 2). In both studies, on the first visit, participants were trained on a Delayed-Response Alphabetization Task (DRAT) in which they alphabetized an array of letters during a delay period. At the end of the delay, a letter with a number above it appeared, and participants indicated whether the number matched the letter position in its reorganized alphabetical order. During the second visit, the DRAT was performed in the MRI scanner to identify individualized rTMS targets, defined as the peak fMRI activation within the l-DLPFC or the l-PC. Electric field (E-field) modeling was used to define the optimal coil position, coil orientation, and stimulation intensity. During the 4 subsequent visits, 5 Hz-rTMS was applied: before the encoding (study 1) and/or during the delay period of the DRAT (study 1, study 2) with either active or sensory-matched electrical sham rTMS. Analysis revealed a significant interaction between difficulty and stimulation in both studies. While active rTMS over the l-DLPFC enhanced accuracy compared to sham, active rTMS over the l-PC significantly reduced accuracy. These opposite effects were found only in the hardest conditions of the DRAT, suggesting a site-, timing- and load-specific rTMS effect. When investigating the predictors of this effect, both fMRI activation and network controllability, the ability of a node to drive the brain between different cognitive states, were found to correlate with the magnitude of improvement associated with active rTMS. These findings provide important information towards the use of rTMS to enhance WM, and potentially a new targeting approach using network controllability which is currently being tested in a new cohort.

Disclosures: L. Beynel: None. **S.W. Davis:** None. **C.A. Crowell:** None. **S.A. Hilbig:** None. **H. Palmer:** None. **A. Brito:** None. **C. Hile:** None. **W. Lim:** None. **D. Nguyen:** None. **M. Dannhauer:** None. **A.V. Peterchev:** None. **R. Cabeza:** None. **S.H. Lisanby:** None. **B. Luber:** None. **L.G. Appelbaum:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

Time: Wednesday, October 23, 2019, 8:00 AM - 10:00 AM

Presentation Number: 637.07

Topic: H.02. Human Cognition and Behavior

Support: NHMRC Grant GNT1072057

Title: Assessing cortical networks involved in working memory using combined transcranial magnetic stimulation and electroencephalography

Authors: *N. ROGASCH, J. MORROW, N. BAILEY, P. FITZGERALD, A. FORNITO; Monash Univ., Melbourne, Australia

Abstract: Working memory is the capacity to hold items in the mind for several seconds and is fundamental for cognitive performance. Animal and human studies have implicated modulation of cortical networks including prefrontal and parietal regions as important for working memory, however assessing how activity propagates through these networks is challenging in humans. Combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) provides a method for non-invasively probing cortical networks during different brain states, such as when engaged in cognitive tasks. In this study, twenty healthy volunteers received TMS to the prefrontal or parietal cortex at rest and while retaining a string of 6 of 8 letters in working memory. EEG was recorded from 62 electrodes and cortical reactivity was assessed by comparing the amplitude of TMS-evoked potentials (TEPs) during rest and working memory using cluster-based permutation statistics. Cortical reactivity differed from rest to working memory following prefrontal cortex TMS, with the largest changes observed between ~70-150 ms and 170-260 ms post TMS ($p<0.001$). Source estimation revealed increased propagation to the fusiform gyrus corresponding to the visual word form area at 80 ms, and reduced propagation to contralateral prefrontal and parietal sites from 100 ms onwards. Similar changes in TMS-evoked activity were observed during working memory following parietal cortex TMS, but only during retention of 8-letters from 100 ms onwards ($p=0.003$). Directly comparing the two sites, working memory-induced changes in TEPs following prefrontal TMS were larger over frontal electrodes compared with parietal TMS for both loads (6 letter, $p=0.016$; 8 letter, $p=0.018$) between 70-100 ms, demonstrating spatial specificity of the effects. Our findings suggest that propagation between the left prefrontal cortex and visual word form area is selectively increased during retention of letters in working memory, and is accompanied by reduced propagation between other cortical regions.

Disclosures: N. Rogasch: None. **J. Morrow:** None. **N. Bailey:** None. **P. Fitzgerald:** None. **A. Fornito:** None.

Nanosymposium

637. The Use of Transcranial Magnetic Stimulation to Modulate Human Memory

Location: Room S402

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Presentation Number: 637.08

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant R01-MH111790
NIH Grant 2T32MH067564

Title: Oscillatory mechanisms for memory encoding tested in humans

Authors: *S. M. LURIE[1], J. L. VOSS[2];
[1]NUIN, [2]Med. Social Sci., Northwestern Univ., Chicago, IL

Abstract: Mechanisms for episodic memory encoding by the hippocampus and functionally connected structures are not fully understood. Hippocampal ensemble activity shows prominent coherence in the theta frequency band, which could serve as a rhythm to orchestrate binding of various sensory inputs into memory. Although computational modeling and limited experimental evidence in rodents suggests that the success of encoding might vary by hippocampal theta phase relative to memoranda, this has not been demonstrated in humans. Our study addresses this question by testing whether theta-patterned transcranial magnetic stimulation (TMS) of the hippocampal-cortical network causes theta-periodic fluctuations in the efficacy of memory encoding. The logic of this design is that if theta-patterned TMS is effective for entraining the hippocampal theta rhythm, then the effectiveness of memory encoding would be expected to vary with the phase of the TMS-entrained theta rhythm. As hippocampus cannot be stimulated directly in humans using noninvasive methods, we stimulated cortical network locations to indirectly influence hippocampal activity, as in other recent work from our laboratory. Immediately following brief (2-second) periods of theta-patterned TMS, we then presented brief (<20ms) associative visual memoranda aligned to the phase of the putative TMS-entrained theta rhythm. Based on previous findings in rodents, we expected periodic fluctuation in memory encoding efficacy as gauged by subsequent recall performance, with best performance for items encoded during the putative TMS-entrained trough and worst performance for items encoded during the putative TMS-entrained peak. We found that memory accuracy varied periodically with stimulation phase. Recall accuracy was best for items encoded during the expected “falling” (peak + $\pi/2$) stimulation phase positions and worst for items encoded during expected “rising” (trough + $\pi/2$) stimulation phase positions ($P<0.1$) for the difference between these phase positions). This periodic effect of stimulation on memory encoding was not identified in a within-subjects control condition that involved the same procedures but with stimulation applied to a location outside the hippocampal-cortical network (vertex). These findings indicate that theta-patterned TMS produces oscillatory entrainment of the hippocampal-cortical network, with a constant phase-lag suggesting latency between stimulation and entrainment of hippocampus and associated structures. Thus, theta phase is relevant for memory encoding in humans and can be manipulated using targeted stimulation.

Disclosures: S.M. Lurie: None. **J.L. Voss:** None.

Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

Location: Room S404

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 638.01

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH (NIMH) #1RF1MH114126-01
NIH (NIDA) #1R01DA036909-01

Title: Human single neuron epigenetics delineates enhancers for specific AAV targeting and cell type-disease mapping

Authors: *J. K. MICH[1], E. E. HESS[1], L. T. GRAYBUCK[1], Y. DING[1], J. T. MAHONEY[1], S. SOMASUNDARAM[1], J. A. MILLER[1], N. SHAPOVALOVA[1], O. FONG[1], S. YAO[1], P. N. CHONG[1], D. BERTAGNOLLI[1], R. D. HODGE[1], T. BAKKEN[1], N. DEE[1], A. H. CETIN[1], K. A. SMITH[1], R. P. GWINN[2], C. COBBS[2], A. L. KO[3], J. G. OJEMANN[4], C. D. KEENE[5], D. L. SILBERGELD[6], V. GRADINARU[7], S. M. SUNKIN[1], H. ZENG[1], E. LEIN[1], B. TASIC[1], J. T. TING[1], B. P. LEVI[1];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Swedish Neurosci. Inst., Seattle, WA; [3]Univ. of Washington Sch. of Med., Seattle, WA; [4]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA; [5]Dept. of Pathology, Univ. of Washington, Seattle, WA; [6]Dept. of Neurolog. Surgery and Alvord Brain Tumor Center, Univ. of Washington, Seattle, WA; [7]Biol. and Biol. Engin., CALTECH, Pasadena, CA

Abstract: A wide variety of cell types comprise the human neocortex, but their roles in normal brain function and disease are largely unknown because few tools exist for their study. Furthermore, the next generation of brain gene therapeutics requires specific reagents for cell type-specific gene expression control. To fulfill these needs, we searched for enhancer elements useful for cell type-specific gene expression. We examined chromatin accessibility in 2858 high-quality single human neocortical nuclei arising from fresh human neurosurgical samples (n = 14 samples). We identified thousands of cell subclass-specific accessible elements displaying both expected and novel transcription factor binding site motifs. These elements frequently are conserved in mouse (34%), often overlap with hypomethylated sites from independent datasets (27%), and can connect cell types with neurological diseases via trait-associated SNPs. We partitioned these cell class-specific open chromatin elements as either “conserved” or “divergent” by comparing human accessible elements to those from mouse. Conserved elements were found to harbor the majority of the heritability for several human brain diseases despite being fewer in number, suggesting that human brain diseases likely involve disruption of conserved expression control elements. Divergent human accessible elements are relatively enriched for several classes of genomic repeats, which suggests a mechanism for evolution of

brain cell type functional elaboration across species. Finally, we demonstrated these accessible elements are often able to drive cell class-specific gene expression reminiscent of their cell class-specific open chromatin pattern in exogenous AAV vectors, suggesting that this dataset harbors many enhancers that can be leveraged to generate vectors that drive cell class-specific gene expression. In summary, we present a catalog of human cell class-specific epigenetic elements, and these elements enable new species-agnostic cell type-specific viral genetic tools, which will illuminate human neuron function and drive gene therapy applications.

Disclosures: **J.K. Mich:** None. **E.E. Hess:** None. **L.T. Graybuck:** None. **Y. Ding:** None. **J.T. Mahoney:** None. **S. Somasundaram:** None. **J.A. Miller:** None. **N. Shapovalova:** None. **O. Fong:** None. **S. Yao:** None. **P.N. Chong:** None. **D. Bertagnolli:** None. **R.D. Hodge:** None. **T. Bakken:** None. **N. Dee:** None. **A.H. Cetin:** None. **K.A. Smith:** None. **R.P. Gwinn:** None. **C. Cobbs:** None. **A.L. Ko:** None. **J.G. Ojemann:** None. **C.D. Keene:** None. **D.L. Silbergeld:** None. **V. Gradinaru:** None. **S.M. Sunkin:** None. **H. Zeng:** None. **E. Lein:** None. **B. Tasic:** None. **J.T. Ting:** None. **B.P. Levi:** None.

Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

Location: Room S404

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 638.02

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: 5U01MH116438-02

Title: Cell type specific chromatin accessibility profiles in the developing human cerebral cortex

Authors: ***R. S. ZIFFRA**[1,2,3,4,5], C. N. KIM[1,2,5], N. AHITUV[3,4], T. J. NOWAKOWSKI[1,2,5,6]; [1]Dept. of Anat., [2]Dept. of Psychiatry, [3]Dept. of Bioengineering and Therapeut. Sci., [4]Inst. for Human Genet., Univ. of California San Francisco, San Francisco, CA; [5]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., San Francisco, CA; [6]Chan Zuckerberg Biohub, San Francisco, CA

Abstract: The developing human cortex contains an astonishing diversity of cell types with distinct and dynamic spatiotemporal gene expression trajectories. Using single cell RNA sequencing we have recently described gene expression landscapes underlying cell fate transitions during human cortical neurogenesis, highlighting programs uniquely initiated at different stages of lineage progression. Sequential expression of transcription factors throughout neurogenesis are alone insufficient to drive the observed diversity in gene expression, which is likely achieved through binding interactions with cell type specific regulatory elements, such as enhancers. However, cell type specific regulatory elements of the developing human cortex have yet to be characterized in a high throughput manner, mainly due to limitations of established bulk

assays for regulatory element discovery that fail to preserve cell type information in heterogeneous tissues. To overcome these limitations, we used recently developed methods to assay chromatin accessibility in thousands of single cells from multiple distinct areas of human cortex throughout development. We identified discrete cell types based on their unique chromatin accessibility landscapes and patterns of accessibility surrounding previously described marker genes. We discovered hundreds of cell type specific putative regulatory elements that reveal master regulators of gene expression trajectories. Taken together, our results show that the cell type specific accessibility of regulatory elements operates as layer of complexity that works with graded expression patterns of transcription factors in a combinatorial fashion to establish distinct and diverse gene expression programs.

Disclosures: **R.S. Ziffra:** None. **C.N. Kim:** None. **N. Ahituv:** None. **T.J. Nowakowski:** None.

Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

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Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH #1RF1MH114126-01
NIH #1R01DA036909-01
Nancy and Buster Alvord Endowment

Title: Neocortical cell class-specific gene expression from AAVs using novel human enhancers

Authors: ***Y. DING**[1], J. K. MICH[1], J. T. MAHONEY[1], E. E. HESS[1], L. T. GRAYBUCK[1], S. SOMASUNDARAM[1], J. A. MILLER[1], N. V. SHAPOVALOVA[1], O. FONG[1], S. YAO[1], P. N. CHONG[1], D. BERTAGNOLLI[1], R. D. HODGE[1], T. E. BAKKEN[1], N. DEE[1], A. H. CETIN[1], K. A. SMITH[1], R. P. GWINN[2], C. COBBS[2], A. L. KO[3], J. G. OJEMANN[4], C. KEENE[5], D. L. SILBERGELD[6], V. GRADINARU[7], S. M. SUNKIN[1], H. ZENG[1], E. S. LEIN[1], B. TASIC[1], J. T. TING[1], B. P. LEVI[1];
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Abstract: The human neocortex is composed of numerous cell types, but their roles in normal brain function and disease are largely unknown because cell type-specific genetic tools for their study have been lacking. To fulfill this unmet need, we are generating new cell class/type-specific adeno-associated virus (AAV) genetic tools that will enable non-species-restricted cell

type functional analysis. These tools leverage high-quality chromatin accessibility profiles (ATAC-seq) from thousands of fresh neurosurgical single human neocortical cells, in order to identify cell subclass/type-specific enhancers. ATAC-seq reveals accessible elements ("peaks") that frequently are conserved in mouse (34%) and likely regulate physiological human brain function. We nominated human-mouse cell class-specific peaks both in proximity to known conserved marker genes and specific peaks not associated with marker genes. We cloned multiple (>100) candidate peaks from both human and mouse genomes, into reporter AAV vectors packaged with mouse blood-brain barrier-penetrant capsid. Several enhancers that drive distinct reporter expression patterns consistent with their expected transcriptomic and accessibility profiles when tested in mouse. Using a combination of immunohistochemistry, hybridization chain reaction (HCR)-amplified multiplexed fluorescence *in situ* hybridization (mFISH), and single cell RNA-seq, we validated that AAV reporter-positive cells frequently mapped to their predicted cell subclasses, including pan-excitatory and pan-inhibitory neurons, and subclass-specific L4, PVALB+, SST+, VIP+, and LAMP5+ cell subclasses. Furthermore, some enhancer-AAV vectors drive specific expression in homologous cell subclasses in both mouse and human neocortical tissue (via human organotypic slice culture transduction). In summary, these findings suggest that ATAC-seq can identify cell subclass-specific enhancers for genetic tools in human and other species. Our newly identified vectors allow the prospective marking and manipulation of certain subclass cells in human for the first time and will fuel more precise gene therapy vectors for unmet clinical needs.

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Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

Location: Room S404

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 638.04

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: R01-MH111529

Title: Identification of enhancers that bestow subtype specific expression of rAAVs in specific neuronal populations

Authors: D. VORMSTEIN-SCHNEIDER[1], J. LIN[1], S. SAKOPOULOS[1], L. ALI IBRAHIM MAROSH[2], O. DEVINSKY[3], J. REYNOLDS[4], G. FENG[5], G. FISHELL[2], ***J. DIMIDSCHSTEIN**[1];
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Abstract: Abnormal development and function of GABAergic interneurons has been implicated in the patho-biology of many neurological and psychiatric disorders. Despite considerable efforts over a number of years, the tools to target and manipulate interneuron function in non-genetically amenable species are very limited. We recently developed a viral strategy that effectively addresses this shortcoming. By using adeno-associated viruses under the control of a short enhancer sequence, we engineered a viral vector that restricts the expression of reporter and effector genes to inhibitory neurons. This approach has proved to reliably target interneurons at all stages of development in mice and also works in a variety of vertebrate species, including birds, ferrets, marmosets and human stem cell derived neurons. This work illustrates the potential of this approach for extending our understanding of interneuron function across a broad range of species, most notably non-human primates. Encouraged by our success in identifying a pan-interneuronal enhancer, we are currently developing a computational method that combines genome-wide mapping of regulatory elements and single-cell RNAseq analysis of the breadth of cortical interneurons. We speculate that systematic screening of these sequences for their ability to direct expression in specific interneuron subtypes will provide a novel approach to target and manipulate particular interneuron subtypes both in developing and mature brain.

Disclosures: D. Vormstein-Schneider: None. **J. Lin:** None. **L. Ali Ibrahim Marosh:** None. **S. Sakopoulos:** None. **G. Fishell:** None. **J. Dimidschstein:** None. **O. Devinsky:** None. **G. Feng:** None. **J. Reynolds:** None.

Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

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Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 638.05

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIGMS R35 GM119831

Title: Parallel functional testing of enhancers in mouse brain

Authors: *L. SU-FEHER[1], J. T. LAMBERT[1], J. L. HAIGH[1], I. ZDILAR[1], L. C. T. BYRNE[2], A. S. NORD[1];
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Abstract: *Cis*-regulatory elements such as enhancers play critical roles in the spatiotemporal regulation of gene expression in the developing brain. The regulatory activity of enhancers is thought to contribute to the development of the vast diversity of cell types in the brain. In addition, sequence variation in enhancers has been linked to genetic risk for neurological disorders such as epilepsy and schizophrenia. Various means of assessing sequences for enhancer activity have been developed; however, it remains difficult to functionally validate predicted enhancers *in vivo*. The advancement of massively parallel reporter assays has enabled large-scale functional screening of enhancer sequences *in vitro* and *in vivo*. We adapted an enhancer reporter assay known as STARR-seq for delivery into the mouse brain using recombinant adeno-associated virus (rAAV) as an expression vector. Results from preliminary deliveries of libraries consisting of disease-relevant predicted enhancers suggest that this method is capable of identifying sequences capable of acting as enhancers in the brain. We validated activity of a schizophrenia-associated regulatory element in the intron of *CACNA1C* using immunohistochemistry to visualize reporter gene expression following delivery of the enhancer reporter construct via *in utero* electroporation or rAAV transduction. This approach enables us to rapidly screen libraries of DNA sequences for enhancer activity *in vivo*, with the further potential to identify sequence variants that contribute to altered gene expression in the brain. Such functional examination of enhancers will be critical toward dissecting the regulatory activity of enhancers in the brain and how enhancer sequence variation contributes to brain development and neurological disorders.

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Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

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Presentation Number: 638.06

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH #1RF1MH114126-01

Title: Comparison and optimization of peak calling software for human temporal cortex single nucleus ATAC-seq data

Authors: *S. SOMASUNDARAM[1], J. K. MICH[1], L. T. GRAYBUCK[2], E. HESS[7], N. SHAPOVALOVA[1], R. D. HODGE[3], T. BAKKEN[1], S. M. SUNKIN[1], R. GWINN[8], C. COBBS[8], A. KO[9], J. OJEMANN[10], C. KEENE[10], D. SILBERGELD[10], H. ZENG[4], B. TASIC[5], E. LEIN[6], J. T. TING[6], J. A. MILLER[1], B. P. LEVI[1];
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Inst., Seattle, WA; [9]Univ. of Washington Sch. of Med., Seattle, WA; [10]Univ. of Washington, Seattle, WA

Abstract: The human neocortex consists of many cell populations that can be classified based on cell shape, firing properties, and gene expression patterns. Recent work at the Allen Institute has identified 75 distinct cell types in human middle temporal gyrus (MTG) using single nucleus RNA-seq. So far, the roles of these cell types in normal brain function and disease has only been hypothesized based on selective expression of specific genes or through matching of homologous types with mouse, where genetic access to cell types is more prevalent. A promising strategy for gaining genetic access to selective human brain cell populations is building viral vectors that leverage regulatory elements (e.g. enhancers) to direct transgene expression in a cell type-specific manner. Single nucleus ATAC-seq provides a strategy for finding Cis Regulatory Modules (CRMs), by identifying areas with chromatin accessibility in cell types of interest. Several software packages have been developed for calling genomic peaks in high-throughput sequencing data and can be used to identify CRMs in ATAC-seq data. Other groups have reviewed these methods for calling peaks in ChIP-seq and DNase-Seq data but there has been no comparison of performance of the peak callers on ATAC-seq data.
We compare the performance of five peak callers (MACS2, Homer, Genrich, F-seq and PeaKDEck) using a broad range of parameter settings on 3 distinct classes of inhibitory neurons from human neocortex (VIP, SST and PVALB). Overall, agreement between the peak callers is quite high. More than 50% of the peaks were called by at least 4 peak callers, suggesting a generally good agreement between methods. We benchmark our human ATAC-seq peaks against the ENCODE project DNase 1 hypersensitivity peaks from adult human frontal cortex. All algorithms performed well at the default settings; however, by varying the thresholds for defining peaks we can improve our overlap with the ENCODE data set (as defined by F-measure). Finally, we cross validate the called peaks against CRMs that have been tested experimentally for specificity in mouse and human interneuron class and report the performance of each method. The entire process is saved as a series of scripts that can be easily applied to assess the performance of peak callers in existing or future ATAC seq data sets.

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Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

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Presentation Number: 638.07

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

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Shurl and Kay Curci Foundation
Hana Jabsheh Initiative to (D.A.L.)

Title: Nuclear lamina-associated genome organization mapping in developing mouse and human brain

Authors: *S. HAMID[1], R. N. DELGADO[3], E. GILL[4], S. HONG[4], A. R. KRIEGSTEIN[2], T. NOWAKOWSKI[4], D. LIM[5];
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Abstract: The three-dimensional organization of mammalian genomes is fundamental to all nuclear processes. The nuclear lamina plays a key role in genome organization and gene expression via its interaction with mammalian chromosomes through lamina-associated domains (LADs). However, due to limitations of previous methods, studies of mammalian genome-lamina associations have been restricted to cultured cell lines, making the organization and dynamics of LADs in cells of the developing brain difficult to assess. To circumvent these limitations, we developed GO-CaRt (GenomeOrganization using CUT and RUN technology) to generategenome-wide maps of LADs in acutely isolated cell lines and tissues including the developing mouse and human brain. Using GO-CaRt, we found that constitutive LADs (cLADs)— those LADs which are broadly conserved across multiple cell types—strongly overlap with those mapped by previous technologies, thereby helping to validate the technology.In addition to the nuclear lamina, we perform additional studies to map genome organization in other nuclear sub-compartments by obtaining genome-wide maps of nucleolus-associated domains (NADs) and speckle-associated domains (SPADs). This approach provided a rich resource for understanding spatial organization of the mammalian genome during brain development.

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Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

Location: Room S404

Time: Wednesday, October 23, 2019, 8:00 AM - 10:30 AM

Presentation Number: 638.08

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Expansive CRISPR/Cas9 mediated genome editing in CNS: A proof of principle for single-neuron genetic labeling and correction of a human gene copy-number variation (CNV)

Authors: M. B. EL-SAADI[1], X. TIAN[1], A. D. RICHARD[1], M. REN[1], K. R. BARTLEY[1], H. SUN[2], R. L. KLEIN[1], ***X.-H. LU**[1];
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Abstract: CRISPR-Cas system has been demonstrated to efficiently correct disease mutations in mouse models, patient-derived tissue, and iPSCs. However, there are three major hurdles for therapeutic genome editing in the central nervous system (CNS): low efficiency of homology-directed repair in post-mitotic neurons, difficulty to achieve cell-type specificity, and delivery. To overcome these hurdles, we have employed a genetic strategy to visualize the genome- edited cells in CNS. Using a neurotropic Adeno-Associated Virus (AAV), we achieved expansive and highly efficient genome editing in postmitotic neurons in adult mouse brains via intravenous systemic administration of a ssAAV:sgRNA. By varying the viral titer, detailed dendrites and axons of the sparsely labeled neurons can be visualized and imaged. We have imaged the neurodegenerative pathology of cortical pyramidal neurons and striatal medium spiny neurons (MSNs) after embolic middle cerebral artery occlusion (MCAO). As a proof-of-principle for therapeutic genome editing, we generated a Bacterial Artificial Chromosome (BAC) transgenic mouse model of human 7q36.3 duplication (triplication) associated with Schizophrenia and Autism. Via intravenous delivery of AAV-sgRNAs, we deleted the whole microduplicated human 7q36.3 genomic regions in mouse brain. The CRISPR/Cas9 mediated single-neuron genetic labeling and perturbation method can be used as an *in vivo* High Throughput Screening (HTS) platform to expedite the understanding of the pathogenesis of neurodegenerative disorders and the development of disease-modifying therapy. With the properties of efficient CNS genome editing in post-mitotic neurons, low risk of insertional mutagenesis, and diminished immune responses, the neurotropic AAV-CRISPR strategy avoids invasive brain surgery and allow therapeutic genome editing to be implemented both safely and effectively for hereditary CNS diseases, such as Huntington's disease and neurodevelopmental disorders.

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Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

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Title: CRISPR based platform for multimodal genetic screens in human iPSC-derived neurons

Authors: *R. TIAN[1], M. GACHECHILADZE[2], C. LUDWIG[1], J. HONG[1], M. WARD[2], M. KAMPMANN[1];
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Abstract: Elucidating gene functions in human neurons is essential for understanding basic neuronal biology as well as identifying mechanisms of human neurological diseases including neurodegenerative and neurodevelopment diseases. However, the limited availability of primary human neurons and the lack of robust genetic perturbation tools impedes the systematic characterization of cellular and molecular functions of genes in human neurons.
Here, we present a CRISPR-based platform that enables large-scale, multimodal functional genomics studies in human neurons derived from induced pluripotent stem cells (iPSCs). We integrated CRISPRi and CRISPRa technology for perturbing gene expression with our previously described i3Neuron method that yields large quantities of highly homogeneous cortical glutamatergic neurons from human iPSCs. We demonstrate robust and durable knockdown or overexpression of endogenous genes using CRISPRi or CRISPRa i3Neurons, respectively. As a proof-of-principle, we conducted three complementary functional genomics studies in such neurons. First, a survival-based screen revealed neuron-specific essential genes and genes that improved neuronal survival upon knockdown. Second, a CROP-seq screen with a single-cell transcriptomic readout uncovered several examples of genes whose knockdown had strikingly cell-type specific consequences. Third, a longitudinal imaging screen detected distinct consequences of gene knockdown on neuronal morphology. Our results highlight the power of functional genomics in human iPSC-derived neurons in establishing casual relationships between genes and phenotypes of interest. This platform opens avenues for the systematic dissection of gene functions and disease mechanisms in different neuronal types.

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Nanosymposium

638. Genomic Engineering Using Enhancers or CRISPR

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Presentation Number: 638.10

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: RSRT Grant 50-1895-0101
Damon Runyon Foundation Fellowship 2164-13

Title: Epigenetic editing to restore MeCP2 in Rett syndrome

Authors: *S. LIU[1], R. JAENISCH[2];
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Abstract: Rett syndrome (RTT) is a devastating neurodevelopmental disorder caused by loss-of-function mutations in the *MECP2* gene on the X chromosome. Most female RTT patients still carry one wild-type allele of *MECP2,* but it is subject to random X chromosome inactivation. RTT-like symptoms can be reversed in RTT adult mice following restoration of *MECP2* expression. Thus, reactivation of the silenced wild-type *MECP2* allele on the inactive X chromosome (Xi) is an exciting research direction with promising therapeutic opportunity. X chromosome inactivation is a classical event mediated by epigenetics. We therefore developed new epigenetic editing tools and applied them to specifically reactivate the wild-type allele of *MECP2* on the Xi and thus to rescue RTT phenotypes. We have reported a DNA methylation editing tool by fusion of a catalytically inactive Cas9 with Tet1 or Dnmt3a (dCas9-Tet1/Dnmt3a) allowing for precisely modification of the methylation status at a given locus (Liu et al, *Cell*, 2016). With application of this editing tool, we studied the hypermethylation of the CGG repeat expansion mutation at the 5' UTR of *fragile X mental retardation 1* (*FMR1)* gene. This mutation causes Fragile X syndrome (FXS), the most common genetic form of intellectual disability in males. We demonstrated that demethylation of the CGG repeats unlocked the epigenetic silencing of *FMR1* and restored FMRP expression in FXS cells. Importantly, epigenetic editing rescued the electrophysiological abnormalities of FXS patient-derived neurons (Liu et al, *Cell*, 2018). To reactivate MECP2 allele on Xi, we generated a new histone acetylation tool that consists of a catalytically inactive Cpf1 (an orthologue of Cas9 with a distinguishable DNA recognition sequence) fused with the core histone acetyltransferase p300, termed as dCpf1-p300. Combination of dCpf1-p300 with dCas9-Tet1 allow for a precise editing of histone acetylation and DNA methylation at the MECP2 locus toward to stable reactivation of MECP2 in RTT neurons.

Disclosures: S. Liu: None. **R. Jaenisch:** None.

Nanosymposium

717. Neurogenesis and Differentiation of CNS Neurons

Location: Room N228

Time: Wednesday, October 23, 2019, 1:00 PM - 2:30 PM

Presentation Number: 717.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: AMED (JP17dm0107130)
AMED-CREST (117597)
KAKENHI JP (15H02358)
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Title: Calcium transients control a morphogenetic cycle underlying neuronal migratory movement

Authors: *S.-I. HORIGANE[1,2,3], S. TAKEMOTO-KIMURA[1,2,3], S. KAMIJO[3], A. ADACHI-MORISHIMA[3], H. FUJII[3], H. BITO[3];
[1]Dept of Neurosci 1, Nagoya Univ, Res. Inst. Environ Med., Nagoya, Japan; [2]Mol Neurosci, Nagoya Univ. Grad Sch. of Med., Nagoya, Japan; [3]Dept of Neurochem, Grad Sch. Med, Univ. of Tokyo, Tokyo, Japan

Abstract: In spite of the critical importance of neuronal migration in the construction of brain architecture and neuronal circuits, morphogenetic rules operating neuronal migration during cortical layer formation have remained elusive. In particular, how numerous neurons can sequentially migrate in succession in a time-orchestrated manner within a limited space remains unsolved. We previously showed that migrating neurons responded to multiple extracellular factors that triggered Ca^{2+} influx via voltage gated Ca^{2+} channels (VGCCs), and further discovered a potential role for VGCC-driven spontaneous regenerative Ca^{2+} transients in neuronal migration. In keeping with this, we here found that radially migrating neurons in the cerebral cortex exhibited repeated spontaneous Ca^{2+} transients, while they underwent a characteristic, transient nuclear deformation or ‘rounding’. Furthermore, an evoked sustained Ca^{2+} elevation was able to trigger such nucleus deformation and maintained it throughout the duration of its transients. Intriguingly, the Ca^{2+} elevation was accompanied with multiple specific nucleus/cell morphology changes during a migratory movement: an initial acceleration followed by a halt in nucleus movement, a retraction in the trailing process, as well as a block in leading process extension. Thus Ca^{2+} elevation regulated three key morphogenetic components of neuronal migration. Mechanistically, Ca^{2+} influx via L-type VGCC and activation of Ca^{2+}/calmodulin-dependent protein kinase Iα (CaMKIα) were essential for nucleus rounding and nucleus movement. Consistently, expression of a dominant L-type VGCC gain-of-function mutation, associated with a syndromic autism spectrum disorder, induced an excessive nuclear rounding and perturbed cell migration. Together, our results shed light on the fundamental role of Ca^{2+} transients in orchestrating multistep morphogenetic cycles underlying neuronal radial migration.

Disclosures: S. Horigane: None. **S. Takemoto-Kimura:** None. **S. Kamijo:** None. **A. Adachi-morishima:** None. **H. Fujii:** None. **H. Bito:** None.

Nanosymposium

717. Neurogenesis and Differentiation of CNS Neurons

Location: Room N228

Time: Wednesday, October 23, 2019, 1:00 PM - 2:30 PM

Presentation Number: 717.02

Topic: A.01. Neurogenesis and Gliogenesis

Title: Regulation of hippocampal morphogenesis and homeostasis by the E3 ubiquitin ligase CRL5

Authors: C. P. CANALES[1], J. S. HAN[2], K. HINO[2], Y. M. CAMARENA[2], Y. HADDADI[2], ***S. SIMO**[2];
[1]CENTER FOR NEUROSCIENCE, UC Davis, Davis, CA; [2]Cell Biol. and Human Anat., Univ. of California Davis, Davis, CA

Abstract: During nervous system development, neurons migrate, mature, and integrate into networks following intricate sets of cues. Similarly, in the adult brain, homeostasis is achieved by responding to cues that regulate a myriad of processes, including the production of new neurons in a process called adult neurogenesis. Cells respond to all these cues by triggering signaling pathways that, at the appropriate time, must be shut off. Inappropriate regulation of signaling pathways causes neurons to migrate to ectopic locations, lose responsiveness to new signals, and/or sustain signaling responses causing harm or death to the cell. The E3 ubiquitin ligase CRL5 is a crucial regulator of neuron migration and cell position in the cortex, cerebellum, and retina by downregulating the Reelin/Dab1 and other signaling pathways. Despite that the CRL5 core components Cullin-5 (Cul5) and Rbx2 are strongly expressed in the hippocampus, the role of CRL5 in the developing and adult hippocampus has not been previously addressed. Our work shows that during development, CRL5 regulates the lamination of the CAs and the dentate gyrus. Depletion of Cul5 or Rbx2 disrupts pyramidal neuron position in a cell-autonomous fashion and affects the morphogenesis of their dendritic tree. Importantly, these effects are independent of the sustained Reelin/Dab1 signaling observed in absence of CRL5 activity. In the dentate gyrus, depletion of Rbx2 causes misposition of granule cells and neural progenitors, which are found in the granule cell layer and hilus. Moreover, CRL5 regulates mossy fiber (the granule cell axon) innervation during late postnatal development. Particularly, we show that depletion of Rbx2 impedes mossy fiber pruning, most likely by hampering Semaphorin-3F signaling. Finally, we show that CRL5 also opposes Reelin/Dab1 signaling in the hippocampus to restrain the production of adult-born neurons in the dentate gyrus. Overall, we identified CRL5 as a novel regulator of hippocampal morphogenesis and homeostasis and uncovered several CRL5-regulated signaling pathways involved in these events.

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Nanosymposium

717. Neurogenesis and Differentiation of CNS Neurons

Location: Room N228

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Presentation Number: 717.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: CURE Taking Flight Award 2018
NARSAD Young Investigator Award 2018

Title: mTOR signaling cell autonomously controls outer radial glial migration in the developing human brain by regulating the length of the basal process

Authors: *L. SUBRAMANIAN, M. ANDREWS, A. R. KRIEGSTEIN;
UCSF, San Francisco, CA

Abstract: The developmental and evolutionary expansion of the neocortex in humans has been attributed to an expanded array of progenitor cells during fetal development. In particular, outer radial glial (oRG) progenitors present in the outer sub-ventricular zone (oSVZ) of the developing human cortex have been proposed to have an important role in this expansion. Recent studies (Nowakowski et al., 2017) have identified high levels of mammalian Target of Rapamycin (mTOR) signaling in oRG cells and suggested that this may be a human-specific adaptation (Pollen et al, 2019). Somatic mutations in the mTOR pathway have also been proposed to cause several malformations of cortical development, by affecting progenitor proliferation, differentiation and migration (Iffland & Crino, 2017). However, we do not yet understand the role played by the mTOR signaling pathway in the development of the human cerebral cortex. We have used *in vitro* models to examine the effects of modulating mTOR signaling during human brain development. Using pharmacological and genetic modulations in organotypic slice cultures, we found that both inactivation and hyper-activation of mTOR signaling resulted in profound changes to the morphology, migration and positioning of outer radial glial (oRG) cells. The basal process of oRG cells was significantly shortened by changing the level of mTOR signaling. Our results suggest that carefully regulated levels of mTOR signaling are vital to the proper morphology of the basal process in oRG cells. We show further that these effects are autonomous to individual oRG cells. We propose that by controlling oRG migration, mTOR signaling plays a vital role in the expansion of the oSVZ during human development and in regulating oRG-dependent neuronal migration.

Disclosures: L. Subramanian: None. **M. Andrews:** None. **A.R. Kriegstein:** None.

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717. Neurogenesis and Differentiation of CNS Neurons

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1R01HD097331-01
1R01DC017149-01

Title: A central role for the transcription factor Gli3 in controlling vomeronasal neurogenesis, formation of olfactory ensheathing cells in the nasal mucosa, and GnRH-1 neuronal migration

Authors: E. M. TAROC[1], A. NAIK[1], J. M. LIN[1], R. BALASUBRAMANIAN[2], ***P. E. FORNI**[1]; [1]Biol., Univ. at Albany, Albany, NY; [2]Harvard, Boston, MA

Abstract: Normosmic idiopathic hypogonadotropic hypogonadism (nIHH) and Kallmann syndrome (KS) are two phenotypic presentations of humans with hypogonadotropic hypogonadism secondary to GnRH deficiency. Growing evidence indicates that KS and nIHH are genetically heterogeneous and are characterized by incomplete penetrance and variable expressivity. Reproductive phenotypes, nIHH and KS subjects commonly exhibit craniofacial defects. In humans, mutations in sonic hedgehog (Shh) signaling, causes a spectrum of craniofacial defects including a short nose with flat nasal bridge and cleft palate. Gli3 is a key transcription factor in controlling Shh intracellular signaling. Gli3 loss-of-function affects the development of the olfactory system. Gli3 expression was found in proliferative cells in the developing vomeronasal area. Analyzing Gli3 extra-toe mouse mutants $Gli3^{Xt/Xt}$ we found reduced neurogenesis in the vomeronasal organ (VNO), defective development of olfactory ensheathing cells in the nasal mucosa, formation of aberrant terminal nerve projections and absence of GnRH-1 neuronal migration in the brain. We found that Gli3 loss of function compromises the generation of Ascl-1 positive neuronal progenitors in the developing VNO, impairs the formation of vomeronasal sensory neurons but not genesis and differentiation of GnRH-1 neurons. Moreover, in Gli3 mutants, we found altered expression of Semaphorin-3A, which is a key guidance cue for GnRH-1 migration. Analysis of Ascl-1 KO mice revealed defective neurogenesis for both VSNs and GnRH-1. The non-overlapping phenotypes between Gli3 and Ascl1 mutants show that Ascl-1 expression is crucial for GnRH-1 neurogenesis, but for these cells is not controlled by Gli3. By analyzing whole exome data from a large cohort of nIHH/KS probands, we also identified several rare *GLI3* variants in humans. Luciferase assays confirmed complete loss-of-function for one novel *GLI3* mutation which was seen in a KS individual who also displayed polydactyly. As a some of the patients carrying rare missense *GLI*3 variants also harbored heterozygous mutations in other KS/nIHH candidate genes we propose that human *GLI3* mutations play an important modifier role and contribute to the oligogenic nature of KS/nIHH.

Disclosures: E.M. Taroc: None. **A. Naik:** None. **J.M. Lin:** None. **R. Balasubramanian:** None. **P.E. Forni:** None.

Nanosymposium

717. Neurogenesis and Differentiation of CNS Neurons

Location: Room N228

Time: Wednesday, October 23, 2019, 1:00 PM - 2:30 PM

Presentation Number: 717.05

Topic: A.01. Neurogenesis and Gliogenesis

Title: PARP1 and its activity is required for oligodendrocyte differentiation during postnatal brain myelination

Authors: *Y. WANG[1,3], S. ZHANG[1,3], B. KIM[1,3], K. FOND[2,3], F. GUO[1,3];
[1]Neurol., UC Davis, Sacramento, CA; [2]UC Davis, Davis, CA; [3]Inst. for Pediatric Regenerative Med., Shriners Hosp. for Children - Northern California, Sacramento, CA

Abstract: In the central nervous system (CNS) development, oligodendrocyte progenitor cells (OPCs) generated from the ventral ventricular zone (VZ) undergo rapid proliferation, migration and differentiation into the myelin-forming oligodendrocytes (OLs), which wraps axons and provides insulation to accelerate the transmission of action potentials. Cell growth and differentiation during developmental processes require the activation of many inducible genes. A number of studies have demonstrated that poly(ADP-ribose) polymerase 1 (PARP1) and poly(ADP-ribosyl)ation, once activated by developmental signals, regulate the transcription and splicing of genes in different cell types and at different developmental stages. However, the function of PARP1 and its activity in OL development has not been defined. We now report that PARP-1 is expressed in OPCs and even highly expressed in newly differentiated OLs, and decreased along with myelination, indicating the regulatory role of PARP1 during OL differentiation. Enzymatically silent PARP1 *in vivo* using 4-hydroxyquinazoline (4HQ) inhibits the activation of PARP1, and attenuates OL formation and differentiation in the developmental forebrain. To prove a cell-intrinsic role of PARP1 in regulating OL differentiation, we isolated primary OPCs and demonstrated that the differentiation of OPCs into OLs is significantly inhibited by PARP inhibitors, 4HQ and PJ34 hydrochloride, and PARP-1-selective inhibitor, BYK204165. Additionally, the primary cultured OPCs from PARP1 null mice showed attenuated differentiation and myelin gene expression, compared with wild-type OPCs. Therefore, our report reveals a previously unappreciated role of PARP1 and its activity in differentiation of oligodendroglial lineage cells in the mouse brain during developmental myelination. Our study points to the potential of manipulating PARP1, activity of PARP1 and its downstream pathways to promote oligodendrocyte development and provides novel therapeutic target for CNS demyelinating diseases.

Disclosures: **Y. Wang:** None. **S. Zhang:** None. **B. Kim:** None. **K. Fond:** None. **F. Guo:** None.

Nanosymposium

717. Neurogenesis and Differentiation of CNS Neurons

Location: Room N228

Time: Wednesday, October 23, 2019, 1:00 PM - 2:30 PM

Presentation Number: 717.06

Topic: A.01. Neurogenesis and Gliogenesis

Title: Developmental establishment of neurons and glia in mouse hippocampus

Authors: *A. M. BOND, D. A. BERG, S. LEE, A. GARCIA, G.-L. MING, H. SONG;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: The hippocampus is a brain region important for learning and memory and can be subdivided into CA1, CA3 and dentate gyrus regions. These subregions develop on distinct timelines, for example the CA1 and CA3 morphogenesis occurs embryonically, while dentate gyrus morphogenesis occurs later during early postnatal development. Previous studies have demonstrated that the timing of neurogenesis in hippocampal subregions follows that of morphogenesis. However, virtually nothing is known about gliogenesis in the developing hippocampus or how developmental differences in gliogenesis may impact glial heterogeneity within the adult hippocampus. Here we used thymidine-analog birth-dating to investigate the timing of neurogenesis and gliogenesis in different regions of the developing hippocampus. EdU was given at a single time point during either embryonic or early postnatal development, followed by a chase period to postnatal day 30 (P30) when all the brains were analyzed. Cells that retained the EdU label at P30 were considered generated by a final cell division at the time point when EdU was administered. Our results confirm that neurogenesis in the CA1 and CA3 regions peaks embryonically, distinct from neurogenesis in the dentate gyrus, which peaks during early postnatal development. Unlike neurogenesis, astrogenesis largely occurred along a similar timeline during the first postnatal week for most regions of the hippocampus, including generation of the quiescent adult radial glia-like stem cells of the dentate gyrus. However, subtle differences in peak astrogenesis occurred according to hippocampal subregion, for example peak astrogenesis in the hilus preceded that in the molecular layer of the dentate gyrus. Our results provide a resource of the developmental generation of multiple cell types in the developing hippocampus and suggest that developmental differences in birthdate may dictate cellular diversity in the adult hippocampus.

Disclosures: A.M. Bond: None. **D.A. Berg:** None. **S. Lee:** None. **A. Garcia:** None. **G. Ming:** None. **H. Song:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.01

Topic: A.07. Developmental Disorders

Support: The Ingeborg Ständer Foundation

Title: Dissecting developmental and transient effects in shankopathies associated with autism spectrum disorders in transgenic mice

Authors: *A. ELTOKHI[1,2], M. HÜSER[1], T. BUS[1], A. ROZOV[3], P. RAO-RUIZ[4], L. L. OETTL[5], A. HARTEN[1], W. KELSCH[5], A. SMIT[4], G. RAPPOLD[2], R. SPRENGEL[1]; [1]Max Planck institute for Med. Res., Heidelberg, Germany; [2]Inst. of Human Genet., Heidelberg, Germany; [3]Inst. of Physiol. and Pathophysiology, Heidelberg, Germany; [4]Fac. of Science, Ctr. for Neurogenomics and Cognitive Res., Amsterdam, Netherlands; [5]Central Inst. of Mental Health, Med. Fac. Mannheim,, Mannheim, Germany

Abstract: The discovery of rare, autism spectrum disorder (ASD)-causing gene variants that alter synapse development and function supports the notion that ASD originates, to a large extent, from synaptic dysfunction (Leblond et. al., 2014). In particular, disruptive mutations in the family of postsynaptic *SHANK* scaffolding genes have been identified in individuals with ASD, collectively summarized as 'Shankopathies'. *Shank* gene deletions revealed some synaptic dysfunctions that were associated with ASD-like behaviors in mouse models. Whether these phenotypes are due to complete functional loss of the gene-targeted SHANK or to a dominant-negative effect of remaining truncated SHANK version(s) remains to be resolved (Eltokhi et. al., 2018). Instead of our previous virus approach (Berkel et. al., 2012), we generated two forebrain-specific conditional transgenic mouse lines to shift the complex SHANK scaffold organization into a scaffold structure, which is predominantly determined by the transgenically overexpressed SHANK2 variants. We aimed to address the following burning questions in the field of ASD: (**A**) What is the direct effect of Shank2 overexpression on synaptic transmission and synapse formation? (**B**) Which ASD symptoms disappear when the genetically-based SHANK dysfunction in the glutamatergic systems is repaired/restored during or after development, and can we use these insights to aid in early detection and prevention of disease progression? (**C**) Which molecular pathways are affected that can provide novel biomarkers for the diagnosis as well as novel therapeutic targets to treat patients with *SHANK2* mutation? Mice of both transgenic SHANK2 lines exhibited autistic-like phenotypes including hyperactivity, anxiety, repetitive and unusual social behaviors. When the SHANK2 dosage was reversed back to endogenous levels in adult mice, specific autistic features were rescued, indicating a certain degree of plasticity in the adult brain. Although ASDs are considered neurodevelopmental disorders, some autistic features were present when the transgenic SHANK2 isoform overexpression was induced after postnatal development. The results of our behavioral, histological, electrophysiological and proteomic analyses will be presented.

Disclosures: **A. Eltokhi:** None. **M. Hüser:** None. **T. Bus:** None. **A. Rozov:** None. **P. Rao-Ruiz:** None. **L.L. Oettl:** None. **A. Harten:** None. **W. Kelsch:** None. **A. Smit:** None. **G. Rappold:** None. **R. Sprengel:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.02

Topic: A.07. Developmental Disorders

Support: DOD AR160091

Title: Forward genetic screen for modifiers of the autism spectrum disorder gene SHANK3

Authors: *J. HOLDER[1], L. WANG[2], F. ANDUJAR-PEREZ[1], L. LIN[1];
[1]Baylor Col. of Med., Houston, TX; [2]UCSF, San Francisco, CA

Abstract: Introduction: *SHANK3* encodes for a scaffolding protein which localizes to the postsynaptic density (PSD) of excitatory synapses. At the PSD, SHANK3 complexes with other proteins such as PSD-95, Homer and the ARP2/3 complex to direct synaptic development and maturation. Depletion of SHANK3 in neurons results in a reduction in synapse formation and neuronal excitability. Deleterious mutations in *SHANK3* are causative of neurological symptoms observed in patients with 22q13 deletion syndrome, Phelan-McDermid syndrome associated with autistic features, developmental delay, and intellectual disability. Adult restoration of wild-type *Shank3* expression in mice has demonstrated behavioral and molecular improvements which opens the door for therapeutic approaches aimed at restoring normal SHANK3 protein abundance. The goal of this work is to identify genetic modifiers of SHANK3 protein stability as potential therapeutic entry points for patients with *SHANK3* haploinsufficiency. **Methods**: Human medulloblastoma (Daoy) cells were infected with a bicistronic DNA construct in which SHANK3 was tagged with GFP and DsRED was expressed from the same transcript (CMV-DsREDiresGFP:SHANK3). Thus, abundance of GFP could be monitored with GFP fluorescence and normalized to DsRED. Pooled CRISPR libraries containing guide RNAs targeting G-protein coupled receptors, kinases/phosphatases or ubiquitin-associated genes were packaged into lentiviral particles and infected into the engineered cell line. The cells were then selected for infection with puromycin and expanded. Cells were then flow sorted with highest and lowest 10% of GFP to DsRED ratio collected for analysis. DNA was isolated from the high and low ratio cells as well as bulk infected cells. Next generation sequencing was performed to identify guides that were depleted or enriched in the hi and lo cells. **Results**: From our primary screen, we have identified four GPCRs, thirteen kinases or phosphatases and greater than 50 ubiquitination related genes that are significantly enriched in our high GFP:DsRED population (FDR <0.01). We are currently further validating these candidates in secondary screens.

Conclusions: CRISPR/Cas9 cell-based screens for protein stability are a novel approach for identifying therapeutic entry points for neurodevelopmental disorders. We have identified a number of candidate regulators of SHANK3 protein stability that could serve as targets for personalized therapies for this autism spectrum disorder.

Disclosures: J. Holder: None. **L. Wang:** None. **F. Andujar-Perez:** None. **L. Lin:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.03

Topic: A.07. Developmental Disorders

Support: IBS-R002-D1

Title: Mode of stimulation matters in rescuing social deficit in Shank2 mutant mice

Authors: *E. LEE[1,2], W. CHOI[5], J. SHIN[3], S. LEE[6], C. CHUNG[4], E. KIM[2,7];
[1]Dept. of Anat., Col. of Medicine, Yonsei Univ., Seoul, Korea, Republic of; [2]Ctr. for Synaptic Brain Dysfunction, Inst. for Basic Sci., Daejoen, Korea, Republic of; [3]Ctr. for Cognition and Sociality, [4]Ctr. for Synaptic Brain Dysfunction, Inst. for Basic Sci., Daejeon, Korea, Republic of; [5]Program of Brain and Cognitive Engineering, Dept. of Bio and Brain Engin., [6]Dept. of Biol. Sci., KAIST, Daejeon, Korea, Republic of; [7]Dept. of Biol. Sci., KAIST, Daejoen, Korea, Republic of

Abstract: Many genes and environmental factors contribute to the development of autism spectrum disorder. But we do not know if there is a common mechanism causing social deficit in many ASDs and if there exist specific neural circuit for a specific social behavior. Excitation and inhibition imbalance of mPFC is a leading mechanism of social deficit. In the medial prefrontal cortex (mPFC) of Shank2 mice, synaptic E/I balance is skewed to excitation but not all optogenetic recovery of E/I imbalance of mPFC rescued social deficit in three chamber test and direct interaction. Only strong pulsatile optogenetic 10Hz stimulation of parvalbumin (PV) interneuron with ChR2 is effective.

Disclosures: E. Lee: None. **W. Choi:** None. **J. Shin:** None. **S. Lee:** None. **C. Chung:** None. **E. Kim:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.04

Topic: A.07. Developmental Disorders

Support: NIMH MH112237
NIMH MH108842

Title: Amelioration of autism-like social deficits by targeting histone methyltransferases EHMT1/2

Authors: *Z.-J. WANG[1], P. ZHONG[1], F. YANG[2], K. MA[1], J.-S. SEO[3], F. ZHANG[1], P. GREENGARD[3], Z. YAN[1];
[1]Physiol. and Biophysics, [2]Biostatistics, The State Univ. of New York At Buffalo, Buffalo, NY; [3]Lab. of Mol. and Cell. Neurosci., The Rockefeller Univ., New York, NY

Abstract: Many of the genes disrupted in autism are identified as histone-modifying enzymes and chromatin remodelers, most prominently those that mediate histone methylation/demethylation. However, the role of histone methylation enzymes in the pathophysiology and treatment of autism remains unknown. To address this, we used mouse models of haploinsufficiency of the *Shank3* gene (a highly penetrant monogenic autism risk factor), which exhibits prominent autism-like social deficits. We found that histone methyltransferases EHMT1 and EHMT2, as well as histone lysine 9 dimethylation (specifically catalyzed by EHMT1/2), were selectively increased in the prefrontal cortex (PFC) of *Shank3*-deficient mice and autistic human postmortem brains. Treatment with the EHMT1/2 inhibitor UNC0642 or knockdown of EHMT1/2 in PFC induced a robust rescue of autism-like social deficits in *Shank3*-deficient mice, and restored NMDAR-mediated synaptic function. Activity-regulated cytoskeleton-associated protein (Arc) was identified as one of the causal factors underlying the rescuing effects of UNC0642 on NMDAR function and social behaviors in *Shank3*-deficient mice. UNC0642 treatment also restored a large set of genes involved in neural signaling in PFC of *Shank3*-deficient mice. These results suggest that targeting histone methylation enzymes to adjust gene expression and ameliorate synaptic defects could be a potential therapeutic strategy for autism.

Disclosures: Z. Wang: None. **P. Zhong:** None. **F. Yang:** None. **K. Ma:** None. **J. Seo:** None. **F. Zhang:** None. **P. Greengard:** None. **Z. Yan:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.05

Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks Family Foundation
MH112237
MH108842

Title: Reversal of synaptic and behavioral deficits in a 16p11.2 duplication mouse model via restoration of the GABA synapse regulator Npas4

Authors: *B. REIN, T. TAN, F. YANG, W. WANG, J. WILLIAMS, F. ZHANG, Z. YAN; Physiol. & Biophysics, SUNY Univ. At Buffalo, Buffalo, NY

Abstract: The human 16p11.2 gene locus is a hot-spot for copy number variations which predispose carriers to a range of neuropsychiatric phenotypes. Microduplications of 16p11.2 are associated with Autism spectrum disorder (ASD), intellectual disability (ID) and Schizophrenia. Despite the debilitating nature of 16p11.2 duplications, the underlying molecular mechanisms remain poorly understood. In the current study, we performed a comprehensive behavioral characterization of 16p11.2 duplication mice (16p11.2$^{dp/+}$) and identified social and cognitive deficits reminiscent of ASD and ID behavioral phenotypes. Furthermore, 16p11.2$^{dp/+}$mice demonstrated deficient GABAergic synaptic transmission and elevated neuronal excitability in the prefrontal cortex (PFC), a brain region critical for high level social and cognitive functions. RNA-sequencing identified genome-wide transcriptional aberrance in the PFC of 16p11.2$^{dp/+}$ mice which included downregulation of the GABA synapse regulator *Npas4.* Restoring *Npas4* expression in PFC of 16p11.2$^{dp/+}$ mice ameliorated the social and cognitive deficits and reversed the GABAergic synaptic impairment and neuronal hyper-excitability. These findings suggest that prefrontal cortical GABAergic synaptic circuitry and Npas4 are strongly implicated in 16p11.2 duplication pathology, and may represent potential targets for therapeutic intervention in 16p11.2 duplication carriers.

Disclosures: B. Rein: None. **T. Tan:** None. **F. Yang:** None. **W. Wang:** None. **J. Williams:** None. **F. Zhang:** None. **Z. Yan:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.06

Topic: A.07. Developmental Disorders

Support: JSPS Grant 26116044
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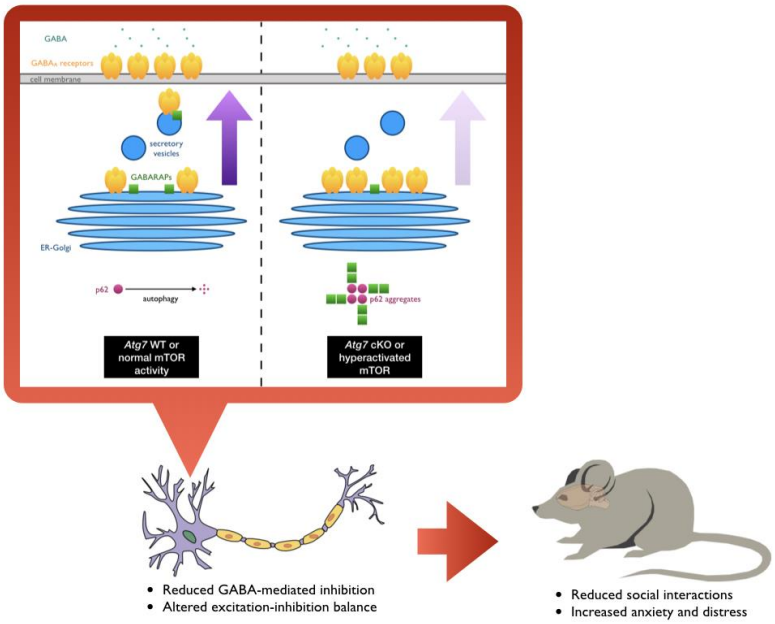
RIKEN Pioneering Projects, Cellular Evolution

AMED Grant JP18H05435
JSPS Fellowship 23-01512
RIKEN Foreign Postdoctoral Researcher program

Title: GABARAPs dysfunction by autophagy deficiency in adolescent brain impairs $GABA_A$ receptor trafficking and social behavior

Authors: *K. K. HUI[1], N. TAKASHIMA[1], A. WATANABE[2], T. E. CHATER[3], H. MATSUKAWA[1], Y. NEKOOKI-MACHIDA[1], P. NILSSON[5], R. ENDO[1], Y. GODA[3], T. C. SAIDO[4], T. YOSHIKAWA[2], M. TANAKA[1];
[1]Lab. for Protein Conformation Dis., [2]Lab. for Mol. Psychiatry, [3]Lab. for Synaptic Plasticity and Connectivity, [4]Lab. for Proteolytic Neurosci., RIKEN Ctr. for Brain Sci., Wako, Japan; [5]Dept. of Neurobiology, Care Sci. and Society, Karolinska Institutet, Huddinge, Sweden

Abstract: Dysfunctional mTOR signaling is associated with the pathogenesis of neurodevelopmental and neuropsychiatric disorders. However, it is unclear what molecular mechanisms and pathogenic mediators are involved and whether mTOR-regulated autophagy continues to be crucial beyond neurodevelopment. Here, we selectively deleted *Atg7* in forebrain GABAergic interneurons in adolescent mice and unexpectedly found that these mice showed a set of behavioral deficits similar to *Atg7* deletion in forebrain excitatory neurons. By unbiased quantitative proteomic analysis, we identified γ-aminobutyric acid receptor-associated protein-like 2 (GABARAPL2) to differentially form high-molecular weight species in autophagy-deficient brains. Further functional analyses revealed a novel pathogenic mechanism involving the p62-dependent sequestration of GABARAP family proteins, leading to the reduction of surface $GABA_A$ receptor levels. Our work demonstrates a novel physiological role for autophagy in regulating GABA signaling beyond postnatal neurodevelopment, providing a potential mechanism for the reduced inhibitory inputs observed in neurodevelopmental and neuropsychiatric disorders with mTOR hyperactivation.



Disclosures: **K.K. Hui:** None. **N. Takashima:** None. **A. Watanabe:** None. **T.E. Chater:** None. **H. Matsukawa:** None. **Y. Nekooki-Machida:** None. **P. Nilsson:** None. **R. Endo:** None. **Y. Goda:** None. **T.C. Saido:** None. **T. Yoshikawa:** None. **M. Tanaka:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.07

Topic: A.07. Developmental Disorders

Support: NJ Governor's Council for Autism Research and Treatment
Nancy Laurie Marks Family Foundation

Title: Autism neural precursor cells in chromosome 16p11.2 deletion syndrome - Defining pathways mediating the hyperproliferation phenotype

Authors: *M. MEHTA[1,2], S. PREM[1], R. CONNACHER[1], M. WILLIAMS[1], L. TURKALJ[1,2], P. MATTESON[2], X. ZHOU[1], E. M. DICICCO-BLOOM[3], J. H. MILLONIG[1,2];
[1]Rutgers Univ., Piscataway, NJ; [2]Ctr. for Advanced Biotech. and Med., Piscataway, NJ; [3]Dept Neurosci & Cell Biol/ Pediatrics (Child Neurol. & Neurodevelopmental Disa, Rutgers Robert Wood Johnson Med. Sch., Piscataway, NJ

Abstract: Chromosome 16p11.2 Deletion Syndrome (16pDS) encompasses a 28-gene deletion contributing to 0.3-1% of idiopathic autism (I-ASD). Individuals with the deletion often present with language disorders, ASD, and macrocephaly - an endophenotype of I-ASD observed in 15-20% of cases. Advances in stem cell technology allow for the study of genetics and neurobiology underlying neurodevelopmental disorders using patient derived cells. For this study we acquired 16pDS iPSCs from the Simons Foundation and control iPSCs from the NIMH. Further, iPSCs from 8 families, including one with severe I-ASD and one unaffected sex-matched sibling control, have been created to compare phenotypes between different autism subgroups. All iPSCs have been induced into neural precursor cells (NPC). Examination of 16pDS NPCs from 3 individuals (2M, 1F) for neurogenesis phenotypes uncovered hyperproliferation defects, including increases in EdU labeling, 3H-thymidine incorporation, and cell numbers. In comparison, proliferation was decreased in two cases from the I-ASD dataset, while hyperproliferation was observed in another family. Interestingly, for the first time, hyperproliferation in both subgroups was correlated with elevated AKT/mTOR activity (increased P-S6 levels), and could be reversed by antagonists, and mimicked by AKT/mTOR agonists in control NPCs. To further distinguish neurogenesis phenotypes between 16pDS and I-ASD, we employed a Luminex QuantiGene Plex Assay to define expression of 24 NPC proliferation genes. While there were few gene differences for I-ASD compared to sibling controls, 16pDS exhibited more than 10 differences, evidence that supports the concept of

different autism subgroups. To begin characterizing 16pDS hyperproliferation, we determined which of the 28 deleted genes were expressed in NPCs. We discovered 15/28 genes are expressed in 16pDS NPCs at ~50% reduced levels; 7 of these genes are linked to the AKT/mTOR pathway. To explore roles of the 15 genes in hyperproliferation, shRNA-mediated knockdowns (kd) have been established in control NPCs. Thus far, *Maz*, MYC-associated zinc finger protein, contributes to increased proliferation post-kd. Once all genes have been identified, rescue over-expression experiments will be performed in 16pDS NPCs, and the effect on AKT/mTOR signaling will be assessed. These studies will aid in identifying the pathways contributing to the 16pDS hyperproliferation phenotype, as well as possible pharmacological interventions. In turn, these insights may have broader relevance to the macrocephaly phenotype and hyperactivated mTOR signaling commonly associated with I-ASD.

Disclosures: **M. Mehta:** None. **S. Prem:** None. **R. Connacher:** None. **M. Williams:** None. **P. Matteson:** None. **X. Zhou:** None. **E.M. DiCicco-Bloom:** None. **J.H. Millonig:** None.

Nanosymposium

718. Autism: Molecular and Cellular Mechanisms

Location: Room S106

Time: Wednesday, October 23, 2019, 1:00 PM - 3:00 PM

Presentation Number: 718.08

Topic: A.07. Developmental Disorders

Support: The Canadian Institutes of Health Research
University of Toronto Faculty of Pharmacy and Centre for Pharmaceutical Oncology

Title: Loss of the DNA repair enzyme oxoguanine glycosylase 1 (OGG1) sex-dependently increases DNA strand breaks and decreases DNA methylation in the brain, possibly contributing to sex-dependent increase in postnatal behavioural disorders

Authors: *S. BHATIA[1], E. ARSLAN[2], P. G. WELLS[1,2];
[1]Pharmaceut. Sci. and Ctr. for Pharmaceut. Oncology, [2]Pharmacol. and Toxicology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Oxoguanine glycosylase 1 (**OGG1**) repairs the reactive oxygen species-initiated DNA lesion 8-oxoguanine, which can alter gene regulation. In humans, OGG1 polymorphisms associate with an increased risk for cancer, diabetes, cataracts, etc., but its role in brain development is unclear. Herein, we investigated in *Ogg1* KO mice the levels of DNA damage [single- and double-strand breaks (**SSBs**, **DSBs**)] via comet assay; epigenetic marks [5-methylcytosine (**5-mC**) and 5-hydroxymethylcytosine (**5-hmC**)] via ELISA-based kits; and brain function disorders at 2-3 months of age via: nesting material shredding and marble burying (repetitive behaviour); novel location and object recognition tests (recognition and spatial

memory); and pre-pulse inhibition (startled response). Cerebellar SSBs were increased in *Ogg1* -/- mice compared to *Ogg1* wild-type (+/+) controls ($p<0.0001$), with no differences in hippocampal levels. However, DSBs were increased in both brain regions of male but not female *Ogg1* -/- mice ($p<0.0001$). Cerebellar 5-mC levels (gene repression marker) were decreased in female but not male *Ogg1* -/- mice ($p<0.05$), whereas in hippocampus a decrease was seen in male but not female *Ogg1* -/- mice ($p<0.0001$). The pattern for 5-hmC was similar to that for 5-mC, with significance in the hippocampus ($p<0.05$). *Ogg1* -/- males showed decreased nesting material shredding compared to *Ogg1* +/+ males, with opposite results in females ($p<0.05$). In contrast, increased marble burying behaviour was seen in *Ogg1* -/- males, ($p<0.05$), with opposite results in females ($p<0.0001$). In novel location recognition tests, at 90 min (not 24 h), *Ogg1* +/+ males and females ($p<0.0001$, $p<0.05$ respectively) but not -/- mice showed the expected preference for objects placed in novel locations. For the novel object recognition test at 24 h (not 90 min), *Ogg1* -/- females but not males showed impaired long-term retention with no preference for the novel object. For startle response, male but not female *Ogg1* -/- mice showed decreased pre-pulse inhibition ($p<0.05$). The OGG1 and sex-dependent increase in DNA damage, decrease in DNA methylation and altered behaviour suggest important novel roles for OGG1 in brain function disorders, possibly including autism (Support: The Canadian Institutes of Health Research; University of Toronto Faculty of Pharmacy and Centre for Pharmaceutical Oncology).

Disclosures: S. Bhatia: None. **E. Arslan:** None. **P.G. Wells:** None.

Nanosymposium

719. Microglial Activation in Disease States

Location: Room S405

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 719.01

Topic: B.11. Glial Mechanisms

Support: VA Merit
AARG

Title: Docosahexaenoic acid (DHA) in the form of lysophosphatidylcholine (LPC) is superior to unesterified DHA in the attenuation of microglial activation *in vitro*

Authors: *D. SUGASINI[1], S. DASARATHY[2], P. C. YALAGALA[1], K. PAHAN[2], P. V. SUBBAIAH[1];
[1]Med., Univ. of Illinois, Chicago, IL; [2]Neurolog. Sci., Rush Univ., Chicago, IL

Abstract: DHA is an essential omega 3 fatty acid that is uniquely concentrated in the brain, and plays a critical role in brain development and function. Its deficiency is known to contribute to neurological diseases such as Alzheimer’s disease (AD). Although plasma DHA is present in

several molecular forms, only unesterified (free) DHA and LPC-DHA have been shown to be transported through the blood brain barrier. The aim of the current study is to determine which of these two molecular forms of DHA is physiologically more effective in the attenuation of microglial activation, a critical component of inflammation-mediated neurotoxicity underlying the various neurological disorders. BV2 microglial cells were incubated with equimolar amounts (100µM) of free DHA, or 1-acyl or 2-acyl isomer of LPC DHA for 24 h, and the DHA content and molecular species composition of DHA-lipids was analyzed by LC/MS/MS. Although the total DHA content of the cells was increased to a similar extent by both free DHA and LPC-DHA, the increases in the cellular phospholipids containing DHA (PC, PE, PS), was 2-3 fold greater after incubation with the two LPC-DHA isomers, compared to free DHA. Both LPC DHA isomers increased the BDNF expression significantly, whereas free DHA had no appreciable effect. Pretreatment of cells with either isomer of LPC-DHA decreased the LPS-stimulated ROS generation by 58%, whereas free DHA decreased it only by 15%. The LPS-induced production of pro-inflammatory eicosanoids (PGE_2, TXB_2, LTB_4) was inhibited by pre-treatment with LPC-DHA by 25-35%, but only by about 10% by free DHA. Similarly, in response to LPS-treatment, the neuroprotectins (NPD1, RVD1, RVD2 and Mar1) were increased by 45-55% in the cells treated with LPC-DHA, but only by about 10-15% in the cells treated with free DHA. Generation of pro-inflammatory cytokines (IL-1ß, IL-6, TNF-α) was inhibited by 45-55% with LPC-DHA, but only by 5-12% with free DHA. These results suggest that LPC DHA exhibits more powerful anti-inflammatory and neuroprotective properties than free DHA in microglia, and that there is no significant difference between the two isomers of LPC-DHA in their beneficial effects.

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Nanosymposium

719. Microglial Activation in Disease States

Location: Room S405

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 719.02

Topic: B.11. Glial Mechanisms

Support: CART Foundation
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Title: Circadian regulation of neuroinflammation and neurodegeneration by Rev-erba

Authors: *P. GRIFFIN[1], J. DIMITRY[2], P. SHEEHAN[2], C. NADARAJAH[2], B. LANANNA[2], E. MUSIEK[2];
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Abstract: Circadian rhythm dysfunction is common to many neurodegenerative diseases. These diseases are also associated with aberrant glial activation. However, clock function in neuroinflammation remains poorly understood. This work demonstrates a role Rev-erbα, a circadian clock component, for regulating neuronal health and neuroinflammation. We observed a diurnal oscillation in hippocampal microglial Iba1 immunoreactivity, which was disrupted in Rev-erbα$^{-/-}$ mice. Rev-erbα deletion in 6-month-old mice resulted in spontaneous astro- and microgliosis as well as increased pro-inflammatory transcript expression in the hippocampus. Primary microglia isolated from Rev-erbα$^{-/-}$ mice exhibited increased proinflammatory mediator expression. However, neither siRNA mediated knockdown nor genetic deletion of Rev-erbα in primary astrocytes led to activation. Transcriptomic analyses from Rev-erbα$^{-/-}$ mice revealed an inflammatory phenotype and suggested dysregulated NF-κB signaling. Accordingly, ChIP analyses showed that Rev-erbα interacts with the promoter region of the *Traf2* gene in primary microglia. This was consistent with increased nuclear translocation of p65 in Rev-erbα$^{-/-}$ microglia. We employed a small molecule Rev-erb agonist (SR9009) to examine the translatability of our work. Rev-erbα$^{-/-}$ mice exhibited increased hippocampal neuroinflammatory responses to peripheral LPS injection, while SR9009 pretreatment suppressed LPS-induced hippocampal neuroinflammation in WT mice. Conditioned media from Rev-erbα-deficient mixed glial cultures exacerbated oxidative damage-mediated cell death in WT neurons, while Rev-erbα$^{-/-}$ mice exhibited reduced resting state functional connectivity, similar to that observed in neurodegeneration. Another prominent feature of neurodegeneration is the loss of synaptic density in the hippocampus. We noted a reduction in the hippocampal CA3 synaptic volume of Rev-erbα$^{-/-}$ mice. Our work establishes Rev-erbα as a novel regulator of CNS inflammation, as well as a link between the circadian clock and glial activation. Rev-erbα may also regulate circadian oscillations in synaptic density. These results warrant future studies investigating the role of Rev-erbα, and broadly the circadian clock in process such as synaptic pruning.

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Nanosymposium

719. Microglial Activation in Disease States

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Presentation Number: 719.03

Topic: B.11. Glial Mechanisms

Support: 1.National Natural Science Foundation of China (NSFC) 81601042

Title: Chronic morphine exposure down-regulated pyroptosis signaling in microglia probably by parkin-related NLRP3 clearance

Authors: *H. WANG, Y. ZHANG, H. LIAO, Y. PENG;
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Abstract: Objective: Morphine is one of the first-line medications for chronic pain, and its clinical usage increases gradually. However, chronic morphine can induce immunosuppression in the central nervous system. Recent studies have found that pyroptosis is also a crucial process mediating inflammation. Whether chronic morphine exposure would lead to pyroptosis dysfunction in microglia is unclear. We aimed to study the changes related to microglial pyroptosis after chronic morphine exposure.**Methods:**Escalating dose of subcutaneous morphine injection for 7 days to C57/6BL mice was used to establish in-vivo chronic morphine exposure mouse model. Both primary mouse microglia culture and microglial cell line BV-2 culture was used in the in-vitro morphine-treated model. Primary mouse neuron culture and astrocyte culture were also investigated in the study. Mouse brain corti and culture cells were collected for extraction of mRNA and proteins. The expressions of mRNA and proteins were detected by qPCR and western-blotting, respectively. Lipopolysaccharides (LPS) was used to activate microglia for priming inflammation and exogenous adenosine triphosphate (ATP) was used to induce pyroptosis of microglia in vitro.**Results:**Morphine treatment increased the expression of total NLRP3 and caspase-1 in the cerebral corti, in primary mouse microglia and microglial BV-2 cells, but not in primary neuron culture or primary astrocyte culture, which indicated that pyroptosis signaling changed in microglia in the central nervous system. In-vitro, LPS-primed and ATP-stimulated primary microglia became swelling and subsequently disrupted, with increasing secretion of LDH and IL-1β, which indicated pyroptosis of microglia. However, morphine-treated microglia showed less swelling and less disruption after LPS- and ATP-stimulating. For BV-2 cell line, although morphine increased NLRP3 and caspase-1 in the non-primed cells, morphine reversed the LPS-induced up-regulation of NLRP3 and caspase-1 in the cells after inflammation priming, and reduced LPS-induced IL-1βsecretion in inflammation-primed BV-2 cells. Furthermore, morphine could reverse the LPS-induced decrease of parkin in the corti and BV-2 cells. Since parkin was reported to related to NLRP3 clearance by mitochondrial autophagy, the above results indicated that morphine may down-regulate pyroptosis signaling in inflammation-primed microglia by parkin-related NLRP3 clearance.**Conclusion:**Chronic morphine exposure down-regulated the LPS-induced pyroptosis signaling in microglia probably by parkin-related NLPR3 clearance.

Disclosures: H. Wang: None. **Y. Zhang:** None. **H. Liao:** None. **Y. Peng:** None.

Nanosymposium

719. Microglial Activation in Disease States

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Presentation Number: 719.04

Topic: B.11. Glial Mechanisms

Support: NIH Grant MH107730

Title: The nuclear GAPDH cascade mediates microglial regulation of cognitive flexibility

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Abstract: Behavioral flexibility is an important behavioral construct that is required for adaptability, and affected under stress conditions. Its disturbance is involved in many neuropsychiatric and neurodegenerative disorders. Excess of oxidative stress has been proposed to play a role in the pathology of these disorders. Therefore, we hypothesized that the nuclear GAPDH (N-GAPDH) cascade,in which GAPDH acts as a sensor of oxidative stress, might play a critical role in regulating behavioral flexibility. To address this question, we used a compound that blocks GAPDH-Siah1 binding, a hallmark of the N-GAPDH cascade activation, without disturbing glycolytic activity [(1R, 3R)-1,3-dymethyl-2-propargyl-1,2,3,4-tetrahidrosiquinoline] ("RR"). First, we found augmented celular autofluorescence in blood cells from schizophrenia patients, compared with those from healthy controls, and is negatively correlated with the behavioral flexibility. The pharmacological intervention of the pathological autofluorescence by "RR" indicates the N-GAPDH cascade may underlie the cellular and cognitive deficits in these patients. To validate this notion mechanistically, we have introduced an animal model that displays cognitive inflexibility and excess oxidative stress (LPS-treated mice). In this model, the N-GAPDH cascade was selectively activated in cortical microglia. Behavioral and biochemical deficits were reverted by "RR". Using unbiased approaches, we depicted a novel mechanism of microglia-neural communication as a downstream of N-GAPDH cascade, which could be responsible for the behavioral deficits. As well, the augumeted autofluorescence observed in the clinic was mimicked in this model. Finally, we genetically validated our results with a conditional knock-in mouse in which the N-GAPDH pathway is silenced only in microglia. We are currently establishing the cellular autofluorescence as a marker for cognitive flexibility and developing a new drug by using "RR" as a lead, which could be applied for not only schizophrenia but also other brain disorders beyond the classical categorical diagnosis. Meanwhile, the novel microglia-neural communication mechanism discovered here could be a new research target to study a fundamental system of neuro-immune interaction.

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Nanosymposium

719. Microglial Activation in Disease States

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Topic: B.11. Glial Mechanisms

Support: NCCIH Grant P50 AT008661-01

Title: Dietary polyphenols mediate resilience to depression and anxiety phenotypes via HMGB1/TLR4/NF-kB danger signaling in the microglia

Authors: *T. FROLINGER, U. IQBAL, S. WESTFALL, C. FREIRE COBO, G. PASINETTI; Icahn Sch. of Medicine, Mount Sinai Med. Cent, New York, NY

Abstract: Exposure to psychological stress can elicit immune responses that confer susceptibility to and anxiety and depressive-like behaviors. Stress causes the release of sterile danger-associated molecular pattern (DAMP), which including high mobility group box 1 (HMGB1), that promotes increased microglia sensitivity via upregulation of toll-like receptors (TLRs), and activation of inflammasome complexes responsible for activating zymogen forms of IL-1β into neuroactive conformations. This pathophysiological pathway plays an important role in driving susceptibility to psychiatric disorders. Here, we show mice treated with a bioactive dietary polyphenol preparation (BDPP) are resilient to stress-induced depression by in part influencing activity of the aforementioned immunological pathway. Mice treated with BDPP were exposed to an unpredictable stress paradigm in which mice were first exposed to stressors for consecutive 28-days (CUS), were given a 28-day post-stress rest (Post-Stress), and were subsequently exposed to a 7-day subthreshold stress paradigm (US). Immediately following completion of the paradigm, mice microglia were isolated and assessed by fluorescent activated cell-sorting (FACS) and immunohistochemistry, and compared to age matched non-stressed, vehicle treated mice (CTRL). We show stress-induced anxiety and depressive behaviors and hyper-ramification of microglia in the amygdala and prefrontal cortex of mice exposed to CUS+US were each attenuated in the BDPP group. We further found BDPP treatment suppressed CUS-induced robust persistent upregulation of *hmgb-1* mRNA ($p<0.05$) and a post stress mRNA upregulation of its receptor, toll-like receptor 4 (TLR4) ($p<0.05$) in enriched microglia. We found BDPP treatment normalized levels of NF-κB activation ($p<0.05$) in response to CUS, and attenuated increased expression of IL-1β ($p<0.05$) protein in the brain following CUS. Treatment with BDPP also suppressed the amplified production of IL-1β in mice exposed to CUS + US ($p<0.05$). Together, our results demonstrate susceptibility to depressive and anxiety behavior in response to stress is in part mediated through priming of microglia via increased *tlr4* and *hmgb-1* expression, increased NF-κB activation, and hyperactive IL-1β secretion, which could each be normalized with BDPP treatment. Our results illustrate how dietary polyphenols provide resilience to stress by influencing the TLR4-NF-κB-IL1β pathway. Further investigations will characterize the specific molecular and genetic substrates metabolites in this pathway our botanical influences to promote resilience to stress.

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Nanosymposium

719. Microglial Activation in Disease States

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Presentation Number: 719.06

Topic: B.11. Glial Mechanisms

Title: Loss of Nrf2 in microglia results in impaired homeostasis and recapitulates a pro-inflammatory subset of disease-associated microglia

Authors: H. C. PARAISO[1], P.-C. KUO[2], B. A. SCOFIELD[2], W.-T. WENG[2], R. D. SWEAZEY[1], J.-H. YEN[2], F.-L. CHANG[3], *I.-C. I. YU[1];
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Abstract: Microglia (MG) represent plastic innate immune cells resident in the central nervous system that can dynamically respond to changes of local brain microenvironment or external stimuli from the periphery. Dysfunctional microglial responses play important roles in the pathogenesis of neurodegeneration including Alzheimer's disease. The nuclear factor (erythroid-derived 2) - like 2 (Nrf2) protein is a transcription factor that regulates expressions of antioxidant and stress defense genes. Here, we reported that chronic deficiency of Nrf2 in MG leads to increased neuroinflammation and cognitive impairment during brain aging. The Nrf2 mRNA transcript was downregulated in aging MG and associated with increased expression of proinflammatory cytokines and complement components. Lack of Nrf2 recapitulates phenotypes of age-associated neuroinflammation and cognitive impairment in mice. Middle-aged Nrf2 knockout (*Nrf2*$^{-/-}$) mice, at 10-12 months-old, showed reactive microgliosis, increased neuroinflammation and infiltration of peripheral immune cells in the brain. The declined learning and memory in middle-aged *Nrf2*$^{-/-}$ mice resembled the cognitive impairment observed in aged (24 months-old) wild-type mice. We found that *Nrf2*$^{-/-}$ MG is hyper-proliferative, showing an increase of surface CD86 expression and nuclear NF-κB p65 translocation at the resting state. *Nrf2*$^{-/-}$ MG had reduced induction of CD206, *Ym1*, and *Fizz1* expressions in response to the IL-4 stimulation. These data suggested that Nrf2-deficient MG are primed toward the inflammatory phenotype and resistant to the anti-inflammatory modulation. In addition, loss of Nrf2 resulted in downregulation of homeostatic signatures, such as *P2ry12*, *Tmem119*, *Fcrls*, *Siglech*, *Gpr34*, and *Tgfbr1* in MG. *Nrf2*$^{-/-}$ MG exhibited upregulated surface markers, Clec7a and CD44, of disease-associated MG (DAM), which is a unique subset of MG identified in Alzheimer's disease. Overall, our results demonstrated the importance of Nrf2 signaling in regulating microglial homeostasis. The functional decline of Nrf2 resulted in dysregulated homeostasis in MG, which might lead to extravagant neuroinflammation and impaired cognitive function in aging and Alzheimer's disease.

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Nanosymposium

719. Microglial Activation in Disease States

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Title: Ketamine anesthetic triggers perineuronal net removal by microglia

Authors: A. VENTURINO[1], R. SCHULZ[1], H. DE JESUS-CORTES[2], F. REILLY-ANDUJAR[2], B. NAGY[1], M. E. MAES[1], G. COLOMBO[1], F. E. SCHOOT UITERKAMP[1], M. BEAR[2], ***S. SIEGERT**[1];
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Abstract: General anesthesia revolutionized modern medicine by allowing drug-inducible, reversible changes of consciousness and cognition. Ketamine is a dissociative anesthetic with a wide range of clinical use in anesthesia, analgesia and sedation, as well as treating psychiatric symptoms, even though it can also cause adverse effects. At the neuronal level, ketamine antagonizes NMDA receptors, which counterintuitively alters synaptic plasticity. We hypothesized that ketamine exploits an unidentified mechanism to exert its effects. Here, we show that ketamine-anesthesia provokes a microglia response that removes the perineuronal net (PNN), a specialized extracellular matrix that restricts neuronal plasticity. Repeated ketamine-anesthesia induces a complete PNN loss initiated in the cortical brain regions, which expands to the hippocampus. Female forerun the effect compared to males. Microglia depletion or blocking the purinergic P2Y12 receptor prevented this phenotype. Our study reveals a new strategy how microglia influences adult brain plasticity without physically removing synapses, and provides new insights into the action of ketamine on the neuronal level.

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Nanosymposium

720. Mechanisms Controlling Retinal Synaptic Connectivity and Function

Location: Room S402

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 720.01

Topic: D.07. Vision

Title: The development of outer retina photoresponsivity

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Abstract: Photoreceptors in the mouse retina express much of the molecular machinery necessary for phototransduction and glutamate release prior to eye opening at postnatal day 12 (P12). We have previously demonstrated light evoked responses of 5 µV from photoreceptors via electroretinogram (ERG) recordings as early as P8. However, it is not known which photoreceptors, rods or cones, are functioning at this time and how these responses may differ throughout development. Further, there is no published data documenting and characterizing the onset and development of bipolar cell physiology.
We recorded a-wave and b-wave responses from dark-adapted mouse retinae at P7, P8, P9, P10 and P30 using ex-vivo ERGs. Cone responses were isolated by first saturating rods with a constant background light (15,000 photons um^{-2} s^{-1}) and subsequently stimulating with test flashes (UV - 365 nm and green-525 nm) (500 - 800,000 photons um^{-2}).
By P8 we detected small a-waves (5 µV) and at each successive day in development, these responses approximately doubled. Total rod and cone response amplitudes were comparable at P10 but prior to this point in development it was difficult to separate responses. The integration times (T_{int}) of these responses were significantly different under background conditions (67 ms - green, 91 ms - UV). By P30 the responses were significantly larger in amplitude (32 µV - green, 38 µV - UV) and the (T_{int}) were significantly different at saturating light intensities (38 ms - green, 60 ms - UV). b-waves were detectable as early as P9 (5 µV) and these b-waves approximately doubled by P10.
The earliest detectable outer retinal photoresponses occur at P8, though data identifying the source (rod or cone) are inconclusive. By P10, photoresponses from outer-retinal photoreceptors are driven both by rods and cones. Differences in cell-specific protein expression patterns may underlie observed differences in green and UV response integration times across development. Light-evoked bipolar cell responses are detectable as early as P9. These data support the hypothesis that the outer retina, including rod, cone and bipolar cells, is functionally responsive to light prior to eye opening, much earlier than previously thought. The development of outer retinal photosensitivity coincides with a critical time in retinal development when light shapes the development of visual circuits. These data provide the first evidence of rod and cone photoreceptor photoresponsivity, and bipolar cell physiology in the postnatal mouse retina.

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Nanosymposium

720. Mechanisms Controlling Retinal Synaptic Connectivity and Function

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Presentation Number: 720.02

Topic: D.07. Vision

Support: R01EY016060
CTSI TL1

Title: cTAGE5 and Tango1 endoplasmic reticulum cargo receptors have complementary but divergent roles in photoreceptors and overall ocular health

Authors: *E. M. CLARK, R. F. COLLERY, H. J. T. NONARATH, J. R. BOSTROM, B. A. LINK;
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Abstract: Millions of individuals are affected by age-related eye diseases, and the prevalence is expected to double between 2010 and 2050 within the United States, as demographics shift towards an older population. Therefore, investigation of factors that affect ocular homeostasis is imperative. Through a genetic screen in zebrafish, we discovered mutations in a gene called *cTAGE5* as a candidate affecting age-related neuronal health. In general, cTAGE5 and a related protein, Tango1, act at the endoplasmic reticulum (ER) for trafficking of large molecules like collagens and lipoproteins, but also can contribute to autophagy. While best characterized in cell culture, their role for maintaining ocular homeostasis in vivo has not been investigated. We hypothesized that within eyes cTAGE5 and Tango1 play important trafficking and/or autophagic roles in neurons to maintain their high metabolic needs, and an important structural role in other tissues of the eye through ECM maintenance. To initiate studies, we generated large deletion mutations within *cTAGE5* and *Tango1* that eliminated most of the coding sequence. Single homozygous mutants show no outward eye phenotypes, but *cTAGE5; Tango1* double homozygous mutants have small eyes. Upon further investigation, we discovered that *cTAGE5* mutants have retinal ganglion cell (RGC) stress as observed by axonal swellings at the optic nerve head and throughout the optic nerve. *cTAGE5* mutants also exhibit lens defects, and most dramatically photoreceptors display ER stress, apparent adhesive defects at the outer plexiform layer, extreme intracellular vesiculation, and stunted outer segment development, followed by age-related photoreceptor degeneration. *cTAGE5; Tango1* double homozygous mutants show exacerbated phenotypes in the lens and photoreceptors. Interestingly, these phenotypes are absent in *Tango1* single homozygous mutants, suggesting complementary, but divergent roles for cTAGE5 and Tango1 in ocular homeostasis. Defects in collagen and lipoprotein trafficking, as well as autophagy, are mechanisms currently under investigation. A thorough understanding of factors essential for ocular homeostasis may provide avenues to decrease the growing burden of eye disease and other age-related neurodegenerations.

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Title: Meta-mosaics in the mammalian retina

Authors: *S. ROY, N. JUN, J. PEARSON, G. FIELD;
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Abstract: The rodent retina has ~30-40 functionally distinct retinal ganglion cell (RGC) types. Each RGC type uniformly tile the visual space with their receptive field (RFs), or, form a RF mosaic. This allows the retina to sample the visual space in a non-redundant manner. The prevailing view is that these RF mosaics are independent of one another in their spatial arrangements. Here, we provide evidence that challenges this view.
We used a multielectrode array (512 electrodes with 60μm pitch) to record simultaneous activity of hundreds of RGCs from individual rat retinas. A checkerboard pattern stimulus was used to classify functionally distinct RGC types and obtain their RF mosaics. To quantify the spatial relationship between mosaics, we employed a novel statistical framework. This involved first reducing each mosaic to a set of points located at the center of mass of the RFs and then calculating the average heterotypic pairwise Coulombic energy by shifting one mosaic with respect to the other. An increase in energy with increasing shift indicates ‘anti-alignment’ i.e. one mosaic filling in pockets of another mosaic; and decrease in energy with increasing shift indicates ‘alignment’ i.e. the two mosaics overlap each other.
We found that RF mosaics of ON and OFF RGC types that form ‘pathways’ (for ex. ON and OFF brisk transient), have minimum energy at zero shift, indicating they are anti-aligned. RF mosaics of ON type RGCs that do not form pathways (for ex. ON brisk transient and ON brisk sustained) are also anti-aligned. In contrast, RF mosaics of OFF type RGCs (for ex. OFF brisk transient and OFF brisk sustained) have maximum energy at zero shift, indicating they are aligned. To ensure these results are robust to mosaic irregularities and defects, we determined the extent to which energy estimates change when RFs are artificially removed and artificially

added. We found minimal change in estimated energy caused by these perturbations, across mosaics of different RGC types. Using an efficient coding model, we further determined that these relationships favor efficiency of coding natural images under realistic constraints imposed by the retina.

These results provide novel evidence for coordination between mosaics of functionally distinct RGC types, suggesting that pathway specific molecular cues may guide coordination during development. Moreover, for a given level of input noise but different levels of output noise (for different cell types), one type of coordination may be favored over another for efficiently coding the joint visual features.

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Title: Transsynaptic modulation of synaptic activity: Leucine-rich repeat protein LRIT1 selectively modulates cone photoreceptor synaptic function

Authors: *Y. WANG[1], I. SARRIA[1], Y. CAO[1], N. T. INGRAM[2], C. ORLANDI[1], N. KAMASAWA[3], A. V. KOLESNIKOV[4], V. J. KEFALOV[4], A. P. SAMPATH[2], K. A. MARTEMYANOV[1];
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Abstract: Mammalian retina consists of different types of neurons wired in a specific fashion which allows complex computation starting early at the first visual synapse formed between photoreceptors (PRs) and bipolar cells (BCs). The information segregation at this synapse is contributed largely by selective wiring of PRs of which the molecular mechanism is not clear. Our previous study discovered that a leucine-rich repeat (LRR) molecule, ELFN1, is necessary for rod PR to rod BC synapse formation by forming a trans-synaptic complex with the post-

synaptic metabotropic glutamate receptor, mGluR6. Given that mGluR6 is used by both rod and cone synapses and that many LRR proteins have been implicated in synaptic connectivity and diversity, it is tempting to speculate that distinct but structurally similar LRR proteins could also contribute to cone synapse formation through similar trans-synaptic mechanism. Here, using unbiased proteomic screening for mGluR6 binding partners, we identified another LRR protein, LRIT1.
IHC revealed that LRIT1 targets to both rod and cone synapses with a significantly higher level in the latter. Both IHC and EM study showed that both rod and cone synaptic structure were intact in LRIT1 KO retina. Electroretinography (ERG) analysis of LRIT1 KO mice under dark-adapted condition showed no significant change in b-wave response. Light-adapted ERG, however, revealed significant reduction in b-wave amplitude in LRIT1 KO mice, suggesting that LRIT1 specifically modulates the light adaptation of cone synapse. Single cell recordings from BCs confirmed the effect of LRIT1 on cone synapse light adaptation and further revealed a signicicant increase in the light sensitivity of both ON- and OFF-cone synapse under dark-adapted condition in LRIT1 KO retinas. Behaviorally, LRIT1 KO mice also showed reduced visual acuity in an optokinetic reflex test. Interestingly, we found that LRIT1 expression level was significantly increased in mice where the pre-synaptic calcium channel complex is severely disrupted, suggesting that LRIT1 might be regulated in a activity-dependent way.
Together, we showed that LRIT1 is a synaptic molecule critical for modulating cone photoreceptor synaptic function through a trans-synaptic mechanism involving both pre-synaptic release machinery and post-synaptic receptors. The current study and our previous works together suggest that various trans-synaptic interaction formed by diverse LRR proteins could serve as a critical molecular determinant for circuit-dependent synaptic formation and function.

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Nanosymposium

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Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 720.05

Topic: D.07. Vision

Support: Academy of Finland 296269 (P.A-L)
Aalto University Centre for Quantum Engineering, CQE (P.A-L)
NIH: EY028111 (FR)

Title: Human vision trades single photons for optimal contrast detection at the sensitivity limit

Authors: M. J. KILPELAINEN[1], A. LAIHI[2], D. TAKESHITA[2], F. M. RIEKE[3], ***P. ALA-LAURILA**[4];
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Abstract: The ability of retinal rods to respond to single photons is a hallmark example of sensory performance approaching the limits of physics[1]. However, the minimum number of photons required for seeing in humans and the neural mechanisms enabling or limiting this number have remained ambiguous. Two recent findings challenge the classical approaches to this question, which rely on the assumption of linear retinal processing: First, the retinal ON pathway - but not the OFF pathway - integrates sparse signals nonlinearly at visual threshold in primates[2]. This nonlinear processing removes much of the noise associated with transmission of signals through the retina at the cost of also removing single-photon responses. Second, the visually-guided behavior of mice can be directly correlated with responses in the ON but not with the OFF pathway in a photon detection task at the sensitivity limit of vision[3]. These two findings lead us to hypothesize that nonlinear signal processing by the retinal ON pathway sets a fundamental limit to the detection of weakest flashes in humans. To test this hypothesis, we quantified the performance of primate ON parasol ganglion cells by single-cell electrophysiology and human observers in psychophysics experiments in matching conditions in two tasks: (1) detecting weak flashes and (2) discriminating between two weak flashes of differing intensities. The retinal thresholding mechanism should limit performance in the first task but not in the second. The performance of human subjects and ON parasol ganglion cells were in close agreement in both tasks. In particular, we find that the threshold for detecting the weakest flash is well above the theoretical limit set by physics, whereas the threshold for discriminating between two weak flashes is considerably lower than that for the detection task, approaching the theoretical limit. Our results show that human visual performance close to threshold is optimized for contrast detection at the cost of losing single-photon responses due to nonlinear signal processing in the ON pathway. Our results require re-evaluating the classical models used to estimate the limiting number of photons required for seeing.
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[1]Hecht, S., Shlaer, S., and Pirenne, M.H. (1942). Energy, quanta, and vision. J. Gen. Physiol. 25, 819-840.
[2]Ala-Laurila, P., and Rieke, F. (2014). Coincidence detection of single-photon responses in the inner retina at the sensitivity limit of vision. Curr Biol 24, 2888-2898.
[3]Smeds, L, Takeshita, D., Turunen, T., Tiihonen, J., Westö, J., Martyniuk, N., Seppänen, A., and Ala-Laurila, P. Paradoxical rules of spike train decoding revealed at the sensitivity limit of vision (submitted).

Disclosures: M.J. Kilpelainen: None. **A. Laihi:** None. **D. Takeshita:** None. **F.M. Rieke:** None. **P. Ala-Laurila:** None.

Nanosymposium

720. Mechanisms Controlling Retinal Synaptic Connectivity and Function

Location: Room S402

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 720.06

Topic: D.07. Vision

Support: NIH F31 EY030344-01

Title: Functional divergence at the MouseType 6 retinal bipolar cell terminal

Authors: *D. SWYGART[1], W. YU[2], S. KNECHT[2], R. WONG[2], G. W. SCHWARTZ[1]; [1]Ophthalmology, Northwestern Univ., Chicago, IL; [2]Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: While neurons were long thought to represent the fundamental computational units of the nervous system, a large body of work over the last 50 years has revealed subcellular functional compartmentalization. We hypothesize that such subcellular compartmentalization in retinal bipolar cells allow individual bipolar cells to transmit different functional signals through different synapses. To test this hypothesis, we examined the output of the type 6 bipolar cell onto two potential downstream retinal ganglion cell types (PixON and On Alpha RGC types).
Light sensitive retinas were extracted from adult mice and whole mounted. Light responses of retinal ganglion cells (RGCs) were recorded under cell attached and whole cell configurations. Dynamic clamp was used to determine the relative contributions of excitatory and inhibitory input. After physiological recording, the retinas were imaged with two-photon microscopy, underwent immunohistochemical labeling and confocal microscopy, or were sectioned and underwent serial electron microscopy. A NEURON model of the type 6 bipolar cell terminal was created using SEM reconstructions.
We show that an individual type 6 bipolar cell is able to provide input with strong surround suppression to the one type of RGC (PixON RGC) while simultaneously providing input with weak surround suppression to a different type of RGC (On Alpha RGC). This subcellular signal divergence occurs at the terminal of the type 6 bipolar cell via GABAergic presynaptic inhibition from wide-field spiking amacrine cells, with our model suggesting that active conductances are essential for providing the subcellular compartmentalization needed for such signal divergence. These findings indicate that each terminal of a single bipolar cell could potentially carry a unique visual signal. This expands the number of visual channels in the inner retina allowing for increased parallelism at the earliest stages of visual processing.

Disclosures: D. Swygart: None. **W. Yu:** None. **S. Knecht:** None. **R. Wong:** None. **G.W. Schwartz:** None.

Nanosymposium

720. Mechanisms Controlling Retinal Synaptic Connectivity and Function

Location: Room S402

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 720.07

Topic: D.07. Vision

Support: NIH R01 EY028915
Thomas C. Rumble Fellowship
RPB Grants
WSU Research Grant

Title: Nicotinic acetylcholine receptors in bipolar cells contribute to motion detection in starburst amacrine cells of the mouse retina

Authors: *C. B. HELLMER, L. M. HALL, C. C. KOEHLER, T. ICHINOSE;
Ophthalmology, Visual and Anatom. Sci., Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: Starburst amacrine cells (SACs) are key neurons for retinal motion detection, sensing objects moving in a "preferred" direction and communicating this information to postsynaptic neurons by releasing both GABA and acetylcholine (ACh). However, the role of ACh release is not yet fully understood. We previously found that a subset of retinal bipolar cells (BCs), Type 7 BCs, express α7 nicotinic ACh receptors (α7-nAChRs). As SACs are the only source of ACh in the retina and receive synaptic input from Type 7 BCs, we examined whether α7-nAChRs in Type 7 BCs contribute to direction selectivity in SACs. We generated a conditional α7-nAChR knockout from Type 7 BCs using a modified Cre-Lox system, Cre-DOG (dependent-on-GFP). Gus-GFP mice (labeling Type 7 BCs) were crossed with floxed α7-nAChR mice and Cre-DOG was introduced via intravitreal AAV injection. To identify α7-nAChR expression, immunohistochemistry was performed using an α7-nAChR marker (α-bungarotoxin, αBtx). Then retinal patch clamp recordings were made from SACs in wildtype or α7-KO mice while giving a moving annulus light stimulus at varying speeds or contrasts. Finally, we generated mice in which SACs express channelrhodopsin-2 (ChR2) to study transmitter release from SACs onto ganglion cells. As Type 7 BCs provide input to ON-SACs, we generated mice of which α7-nAChRs were eliminated from Type 7 BCs to ascertain their role in SAC direction selectivity. In these mice, α-bungarotoxin did not label Type 7 BCs in contrast to wildtype mice indicating the knockout was successful. Patch clamp recordings from ON-SACs revealed that directional tuning is significantly reduced in the Type 7 BC α7-nAChR knockout mice, and that furthermore non-linearities in the SACs responses were reduced as well. When these signaling changes were simulated using ChR2, we observed impaired transmitter release to ganglion cells. When α7-nAChRs are knocked out of Type 7 BCs, SACs' ability to distinguish between preferred and null direction object motion is significantly reduced and their transmitter release is impaired. We have shown for the first time that acetylcholine receptors in a subset of bipolar cells contribute to SACs' direction selectivity.

Disclosures: C.B. Hellmer: None. **L.M. Hall:** None. **C.C. Koehler:** None. **T. Ichinose:** None.

Nanosymposium

721. Integration Across Sensory Modalities

Location: Room S403

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 721.01

Topic: D.09. Multisensory Integration

Support: Wellcome Trust Senior Investigator Award (098433)

Title: Rhythmic modulations in representational interactions between audiovisual speech features

Authors: *H. PARK[1], R. A. A. INCE[2], J. GROSS[3,2];
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Abstract: Network processing of complex naturalistic stimuli requires moving beyond the mass-univariate analysis of simple statistical contrasts to use methods that allow us to directly quantify representational interactions, both between different brain regions as well as stimulus features or modalities. In our recent work, we quantified representational interactions in MEG activity between dynamic auditory and visual speech features, using an information theoretic approach called the Partial Information Decomposition (PID). We showed that both redundant and synergistic interactions between auditory and visual speech streams are found in the brain, but in different areas and with different relationships to attention and behaviour. In the current study, we aimed to investigate how these two interactions aforementioned as well as unique information can be characterized spatiotemporally. We computed redundant, synergistic and unique information between dynamic auditory and visual sensory signals about the ongoing MEG activity localised to pre-defined anatomical regions (AAL; Automated Anatomical Labeling). We first found that behaviourally relevant synergistic information has shown differentially in primary sensory areas and higher-order areas when participants paid more attention to matching audiovisual speech while ignoring an interfering auditory speech. In primary visual and auditory areas, synergistic interaction depends on low-frequency rhythmic fluctuation as a function of auditory delay. However, in inferior frontal and precentral areas, synergistic interaction depends on low-frequency fluctuation as a function of visual delay. Second, the involvement of rhythmic fluctuation of auditory unique information as a function of auditory delay is shown in the right primary sensory areas (auditory, visual). This was critical for speech comprehension. The current method allows us to investigate multi-sensory integration in terms of explicitly quantified representational interactions: either overlap or common information content (redundancy), or superlinear interactive predictive power (synergy), as well as the unique information provided by each modality feature alone. We hope this framework can

provide a more detailed view of cross-modal stimulus representation and hence give insight into the cortical computations which process and combine signals from different modalities.

Disclosures: H. Park: None. **R.A.A. Ince:** None. **J. Gross:** None.

Nanosymposium

721. Integration Across Sensory Modalities

Location: Room S403

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 721.02

Topic: D.09. Multisensory Integration

Support: NIH R00DC012065
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Klingenstien-Simons Foundation
Sloan Foundation
McKnight Foundation

Title: Nonlinear integration of multisensory orientation cues in the *Drosophila* central complex

Authors: *T. A. CURRIER, A. M. LICATA, A. M. M. MATHESON, K. I. NAGEL; Neurosci. Inst., New York Univ. Med. Ctr., New York, NY

Abstract: To locate food, mates, and shelter, animals must find their way through complex multisensory environments. Despite the importance of this behavior, the brain mechanisms that integrate navigation cues across multiple sensory modalities are not well understood. In insects, many sensory-guided navigation tasks rely on a brain region known as the Central Complex (CX), and recent work has demonstrated that multiple sensory modalities may be represented in this area. To assess the multisensory capacity of CX neurons, we used whole-cell patch clamp recordings in awake fruit flies (*Drosophila melanogaster*). We recorded the responses of identified fan-shaped body (FB) columnar neurons to directional stimuli from three modalities: vision (a high-contrast stripe), mechanosensation (airflow), and olfaction (apple cider vinegar). Each of these stimuli has been previously shown to elicit orienting behavior. We observed that many ventral FB columnar neurons were tuned for airflow ("wind") direction. Trans-tango experiments suggest that these neurons receive input from a wind direction-computing pathway previously described by our lab. Wind responses in FB columnar neurons were enhanced in a nonlinear way by the addition of stimuli from other modalities. The sensory modalities that altered wind tuning varied according to the precise FB lamina innervated by the recorded neurons. We used video monitoring of experimental flies during stimulus presentation to rule out the possibility that the neural activity we observed was related to movement. FB columnar neurons therefore provide a plausible substrate for the integration of navigation-relevant multisensory cues within the CX. Ongoing work is aimed at understanding the circuit, synaptic,

and cell-intrinsic mechanisms that underly the nonlinear response changes that we observed in FB columnar cells.

Disclosures: T.A. Currier: None. **A.M. Licata:** None. **A.M.M. Matheson:** None. **K.I. Nagel:** None.

Nanosymposium

721. Integration Across Sensory Modalities

Location: Room S403

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 721.03

Topic: D.09. Multisensory Integration

Title: Visually induced motion sickness is reduced by synchronous engine sounds and vibrations in a motorcycle simulator

Authors: *K. AIGO[1], Y. ITAGUCHI[1,2], M. HAYASHI[1], Y. SAWADA[1], T. MIYAGI[2], T. UEDA[2], M. MIKI[3], T. KIMURA[3], M. MIYAZAKI[1,2];
[1]Dept. of Computer Sci., Shizuoka Univ., Hamamatsu, Japan; [2]Dept. of Informatics, Grad. Sch. of Integrated Sci. and Technology, Shizuoka Univ., Hamamatsu, Japan; [3]YAMAHA MOTOR Co., Ltd., Iwata, Japan

Abstract: Driving simulators are useful for the evaluation and improvement of driving skills; however, they induce simulator sickness, a type of visually induced motion sickness (VIMS). VIMS is explained by the sensory conflict theory, which assumes that motion sickness is caused by a mismatch between the actual and stored neural signals. Based on this theory, we hypothesized a reduction in VIMS by presenting engine sounds and vibrations, in synchronization with the visual experience of the motorcycle simulator. To test our hypothesis, the severity of VIMS was compared between two groups, audio-vibration (AV) and no-audio-vibration (no-AV). The participants, seated on a stationary motorbike (Figure 1a), experienced a 5-minute driving scene from a first-person viewpoint (Figure 1b) with or without the engine sounds and vibrations. The scene was projected on a head-mounted display. We used fast motion sickness scale (FMS) and simulator sickness questionnaire (SSQ) to assess VIMS. FMS was recorded by the participants' verbal response of a number between 0 to 20 as a measure of severity of the current motion sickness every minute of the experiment. SSQ was measured after the experiment by assigning a score between 0 and 3 for 16 items. The score of FMS and SSQ was lower in the AV group than in the no-AV group. We conducted a two-way analysis of variance for FMS and a t-test for SSQ to assess the group effect. The results indicate significantly lower FMS and SSQ scores in the AV group than in the no-AV group. In accordance with the sensory conflict theory, our finding suggests that synchronous presentation of multimodal stimuli associated with reality reduces VIMS.

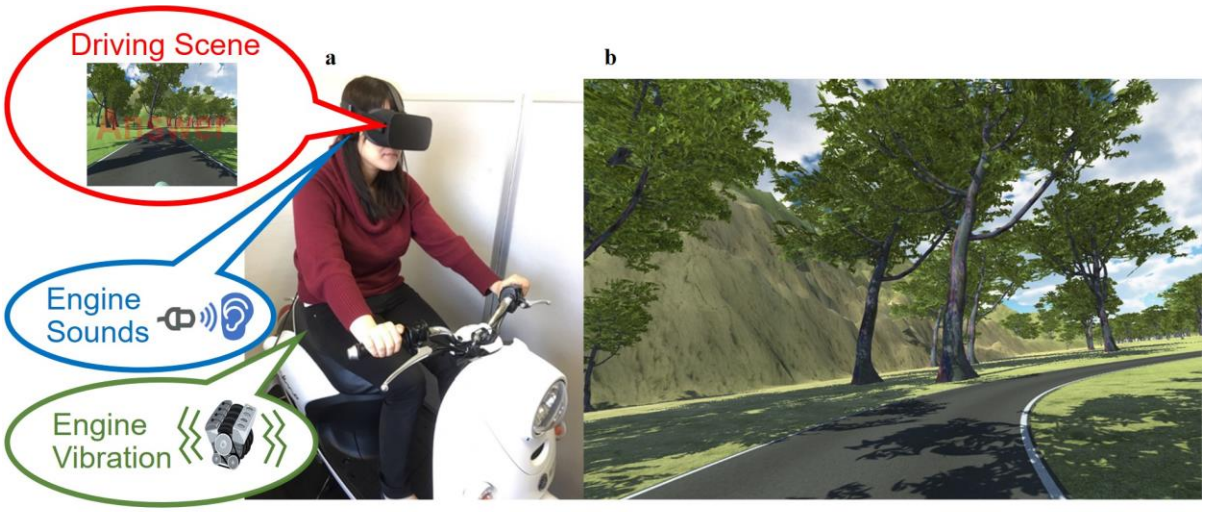

Figure 1. Experimental settings. (**a**) Motorcycle simulator. (**b**) Driving scene.

Disclosures: **K. Aigo:** None. **Y. Itaguchi:** None. **M. Hayashi:** None. **Y. Sawada:** None. **T. Miyagi:** None. **T. Ueda:** None. **M. Miki:** None. **T. Kimura:** None. **M. Miyazaki:** None.

Nanosymposium

721. Integration Across Sensory Modalities

Location: Room S403

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 721.04

Topic: D.04. Somatosensation – Touch

Support: National Key Research and Development Program Grant 2016YFF0201002

Title: Pure haptic training enhances visual executive attention

Authors: ***Y. LUO**, J. ZHANG;
Beihang Univ., Beijing, China

Abstract: Executive attention is a crucial component for appropriate cognitive functioning. Increase the ability for maintaining executive attention may help prevent attention related cognitive impairment. Previous studies have shown that executive attention can be improved by visual cognitive trainings. However, it remains unknown whether haptic training can contribute to executive attention. Here we used high-density electroencephalography (EEG) in 34 human participants (both sexes), in combination with source localization and functional connectivity methodologies, to explore the possibility and underlying neural mechanisms of haptic training effects on visual executive attention. We found that participants with pure haptic training outperformed nontrainees in executive attention in the Attention Network Test (ANT). We also found that this phenomenon was associated with N200 and P300 effects, namely, N200

amplitude reductions, P300 latency reductions and P300 amplitude enhancements. Source localization analyses identified stronger activation in sensorimotor regions at N200 and in prefrontal regions at P300 in the trainees. Furthermore, we observed a left temporal advantage in the trainees at P300. Additionally, pure haptic training was found to enhance the functional connectivity between frontal-parietal exchanges in the beta band at P300. Our results suggest cross-modal transfer benefits of pure haptic training, and reveal that improved executive attention through this training may rely on hierarchical processing, including stronger functional connectivity of the frontoparietal network and finer representation in the sensorimotor and prefrontal cortices, which are regions involved in top-down sensorimotor integration and conflict resolution. These findings may help illustrate the potential use of haptic training in attention enhancements and cognitive impairment amelioration.

Disclosures: Y. Luo: None. **J. Zhang:** None.

Nanosymposium

721. Integration Across Sensory Modalities

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Topic: D.09. Multisensory Integration

Support: Wellcome Trust WT092606AIA
BBSRC BB/J009849/1
European Research Council ERC CoG-MECHIDENT
NIH R01-DC04290
NIH UL1-RR024979

Title: Amodal neural representations and face and voice coding principles in the human brain

Authors: Z. KOCSIS[1], R. S. MUERS[2], H. KAWASAKI[1], T. D. GRIFFITHS[2], M. A. HOWARD, III[1], ***C. I. PETKOV**[2];
[1]Dept. of Neurosurg., Univ. of Iowa Hosp. and Clinics, Iowa City, IA; [2]Med. Sch., Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: Amodal representations are those associated with unique entities that are consistent across any form of sensory input (e.g., hearing the voice of an individual, seeing their face or both). Such representations are important for forming abstract concepts and for identifying neural coding principles. A dominant hypothesis is the “hub-and-spoke” model, whereby modality-specific information from sensory cortices (“spokes”) feeds into modality invariant convergence sites (“hubs”). However, the neurophysiological bases for amodal representations are unknown, and we examined the hypothesis that neural amodal representations are distributed across sensory cortex and convergence sites. Additionally, we sought to better understand the

face and voice coding principles in the human brain. We studied neural responses in intracranial recordings from human epilepsy patients being monitored for epilepsy treatment. The participants were presented with dynamic auditory (voice), visual (face), and audio-visual (combined face-voice) stimuli, which were morphed between exemplar identities or through an average identity (prototype). Amodal responses were identified using a vector similarity analysis of local-field potential (LFP) responses to the stimuli in any sensory modality. The Euclidean distance between all combinations of auditory, visual and audio-visual stimuli was cast as a vector and converted to a normalised Amodal Similarity Index (ASI). A response component was categorised as amodal if the ASI value was <5%, indicating a high level of similarity across all stimulus combinations. Time-frequency based analyses showed a substantial proportion of recording sites throughout regions of the temporal lobe that displayed amodal responses. However, the time-frequency patterns were strikingly different between sites with regards to the timing and prominence of amodal response components in the gamma or lower frequency ranges. We also present results on the norm and exemplar coding properties of the human temporal lobe. In conclusion, amodal representations appear to be more broadly distributed than suggested by the "hub-and-spoke" model and are differently reflected in neurophysiological response patterns in auditory and association cortices.

Disclosures: Z. Kocsis: None. **R.S. Muers:** None. **H. Kawasaki:** None. **T.D. Griffiths:** None. **M.A. Howard:** None. **C.I. Petkov:** None.

Nanosymposium

721. Integration Across Sensory Modalities

Location: Room S403

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 721.06

Topic: D.09. Multisensory Integration

Title: Empirical evidence for the effectiveness of the Z-Bell test in measuring non-image-forming retinal input channels

Authors: *D. G. ZELINSKY[1], C. ELLIOTT[2];
[1]Res., The Mind-Eye Inst., Northbrook, IL; [2]DePaul Univ., Chicago, IL

Abstract: The Z-Bell[SM] test--which measures the functioning of non-image-forming retinal input through closed eyelids--has been in neurodevelopmental optometric clinical use for more than 25 years. The test is thought to be particularly sensitive in measuring the functional properties of the 12,000 intrinsically photosensitive retinal ganglion cells (ipRGCs) in each eye and their relationship to both the autonomic and central nervous systems. The non-image-forming retinal channels affect how we perceive context in the space around us when forming visual imagery, and is linked to the 3D visual/spatial interpretation of auditory input and to proprioceptors. By using therapeutic eyeglasses and pitched bells, we can measure changes in a

subject's spatial processing, and remediate deficiencies among non-image-forming neural channels that operate in even the low-light conditions produced by closed eyelids.
Despite the 25-year clinical history of the test, and its effective use in more than 4,000 post-concussive syndrome (PCS) cases, there is a lack of empirical evidence showing the specific testing effects. In a carefully controlled, repeatable, double-blind study--with full IRB approval & certifications for all principles--we used video cameras to record x, y position on 96 Z-Bell test data points for each of 14 subjects to gather preliminary data from a larger study (N=38). For this report coders examined ~126,000 still images from the video, with 1/2 inch unit overlay grids to measure how close subjects came when reaching for pitched bells in the various test conditions. One of our hypotheses was that subjects (with eyes closed throughout) would do better at locating and reaching for the rung bells in space around them with prescription eyeglasses designed to make them comfortable in their non-image-forming retinal processing, than they would with otherwise identical glasses that had neutral (clear glass) non-prescriptions. As predicted, a statistically significant difference was found when comparing the distances in the two conditions, $t(27) = 2.12$, $p < .05$, $d = .404$. [Avg Neutral Rx distance = 5.06 units (sd=2.33); Avg improved Rx dist = 4.42 units (sd=2.31).]

Disclosures: D.G. Zelinsky: None. **C. Elliott:** None.

Nanosymposium

721. Integration Across Sensory Modalities

Location: Room S403

Time: Wednesday, October 23, 2019, 1:00 PM - 2:45 PM

Presentation Number: 721.07

Topic: D.09. Multisensory Integration

Title: Mesoscale calcium activity imaging of the whole cortex in freely behaving mice

Authors: *M. L. RYNES[1], D. SURINACH[2], M. LAROQUE[2], J. DOMINGUEZ[2], L. GHANBARI[2], G. JOHNSON[2], S. B. KODANDARAMAIAH[2];
[1]Biomed. Engin., [2]Mechanical Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: The advent of genetically-encoded calcium indicators, along with surgical preparations such as thinned skulls (Drew et al Nature Methods 2010) or refractive index matched skulls (Silasi et al Nature Methods 2016), have enabled mesoscale cortical activity imaging in headfixed mice. Such imaging studies have revealed complex patterns of coordinated activity across the cortical surface during spontaneous behaviors (Mohajerani et al Nature Neurosience 2013), goal-directed behavior (Allen et al Neuron 2017), locomotion (Musall et al Biorxiv 2018), motor learning (Makino et al Neuron 2017) and perceptual decision making (Orsolic et al BiorXiv 2019). However, studies have shown that neural activity during free, unrestrained behavior significantly differs from that recorded in headfixed animals. Furthermore, freely moving animals exhibit a repertoire of behaviors that is vastly increased from headfixed

animals. The ability to perform mesoscale imaging of the cortex in freely behaving mice will potentially open up new avenues of scientific enquiry.
Here we present the 'Mesoscope', a miniature, head-mountable imaging device compatible with transparent polymer skulls recently developed by our group ('See-Shells', Ghanbari et al Nature Communications 2019). With a 8x10 mm field of view, the Mesoscope can image most of the mouse dorsal cortex with resolution rangin from 39.37 to 55.68 micrometers. The current prototype weighs 3.4g, and incorporates a magnetic interlocking mechanism that allows quick fixation (<1s of temporary restraint) to a See-Shell implanted on an awake mouse. Open Field behavior tests indicate neither See-Shell implantation nor addition of Mesoscope significantly inhibits locomotion. The mesoscope employs an array of blue LEDs to illuminate the cortical surface uniformly, with up to 8mW of light power. An additional green LED provides illumination for reflectance imaging of intrinsic optical signals arising from changes in cortical blood volume and oxygenation. We have used the Mesoscope to successfully record mesoscale cortical activity of the whole cortex in freely behaving mice, revealing intriguing coordinated activity patterns across cortical regions during a wide variety of behaviors which would be difficult to study in headfixed animals.

Disclosures: **M.L. Rynes:** None. **D. Surinach:** None. **M. Laroque:** None. **J. Dominguez:** None. **L. Ghanbari:** None. **G. Johnson:** None. **S.B. Kodandaramaiah:** None.

Nanosymposium

722. Cortical and Subcortical Planning and Execution

Location: Room N227

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 722.01

Topic: E.04. Voluntary Movements

Support: NIH Grant R01 DC014358
NIH Grant R21 DC016135

Title: Dose-dependent effects of methylphenidate administration on 50-kHz ultrasonic vocalizations in adult male rats

Authors: *S. A. LECHNER, C. A. KELM-NELSON, M. R. CIUCCI;
Dept. of Surgery, Div. of Otolaryngology, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Rodent ultrasonic vocalizations (USVs) are commonly used to study the neurobiology of vocal behavior as well as communication dysfunction in neurodegenerative diseases such as Parkinson disease (PD). Emission of affiliative 50-kHz USVs is modulated by various classes of drugs that alter catecholamine systems. Methylphenidate, a CNS stimulant similar to amphetamine, modulates levels of dopamine and norepinephrine by binding to their respective transporters and blocking reuptake. However, it is not yet completely understood how

methylphenidate affects vocal communication in rodents. This study analyzed the dose-dependent effects of methylphenidate on acoustic (intensity, bandwidth, peak frequency, and duration) and non-acoustic (call rate and subtype profile) parameters of 50-kHz USVs in adult male rats. We hypothesize that increasing doses of methylphenidate will significantly alter these acoustic and non-acoustic features. To test this, ten male Long-Evans rats, aged 12 months, received an acute intraperitoneal administration of methylphenidate (0, 2.5, 5, 7.5, 10 mg/kg) in a counterbalanced design. Male USVs were recorded and analyzed by two masked raters. A one-way analysis of variance (ANOVA) was used to determine statistically significant differences in the acoustic and non-acoustic features of 50-kHz USVs for each of the doses compared with vehicle. Although none of the observed data sets were significant, preliminary data suggest call rate and frequency modulated (FM) call duration dose-dependently increase with methylphenidate administration. Conversely, FM intensity indicated a U-shaped relationship, while call complexity data appear to demonstrate an inverted U-shaped relationship. The complete data set will include a comparison to a Parkinsonian rat model as well as influences of methylphenidate administration on sensorimotor function and anxiety. In general, these results suggest that methylphenidate impacts the acoustic and non-acoustic variables of 50-kHz USVs.

Disclosures: S.A. Lechner: None. **C.A. Kelm-Nelson:** None. **M.R. Ciucci:** None.

Nanosymposium

722. Cortical and Subcortical Planning and Execution

Location: Room N227

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 722.02

Topic: E.04. Voluntary Movements

Support: Bootes Medical Research Foundation

Title: What can the rat dorsal column nuclei tell us about the limits of human tactile perception?

Authors: R. CHEUNG, C. WALTERS, A. J. LOUTIT, R. M. VICKERY, I. BIRZNIEKS, ***J. R. POTAS**;
UNSW Sydney, Sydney, Australia

Abstract: Tactile events that translate into a conscious experience must travel through the Dorsal Column Nuclei (DCN). Here patterns of impulses in the sensory afferents are transformed during synaptic transmission to second-order projection neurons of the DCN. The precise nature and purpose of these transformations are not well understood, however there is evidence that short-interval bursts of impulses in peripheral afferents may cause only a single impulse to propagate in DCN projection neurons. Defining the temporal limits on this burst processing will facilitate understanding of tactile neural encoding. We aimed to determine these temporal limits using psychophysical experiments in human subjects, and single unit neural recordings from the

DCN in urethane-anesthetised rats (ethics approval ACEC19/19A and HREC16245, UNSW Sydney). Pulsatile mechanical stimuli were employed in both experiments that enabled time-controlled generation of single impulses in a fixed population of tactile afferents arising from the glabrous skin of human and rat digits. Human subjects made perceptual judgments about the number of mechanical pulses delivered. The identical stimuli were presented to rats whilst recording neuronal responses using a multi-electrode array in the DCN. We found that the capacity for humans to perceive two distinct mechanical pulses with small inter-pulse intervals aligned closely with the ability of projection neurons in the rat DCN to generate a second neuronal response to these same stimuli. These findings suggest that neuronal responses from the rat DCN are consistent with limits on human perceptual performance, and that this may represent an appropriate model to further explore tactile neural encoding.

Disclosures: **J.R. Potas:** None. **R. Cheung:** None. **C. Walters:** None. **A.J. Loutit:** None. **R.M. Vickery:** None. **I. Birznieks:** None.

Nanosymposium

722. Cortical and Subcortical Planning and Execution

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Topic: E.04. Voluntary Movements

Support: NIH R01NS095162
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Title: Sensory computations in the cuneate nucleus of macaques

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Abstract: A central question in neuroscience is how sensory representations are transformed as they ascend the neuraxis. In primates, the coding of tactile information has been extensively studied in primary afferents and in somatosensory cortex (S1). The general picture that emerges from this previous work is that the responses of neurons in S1 explicitly encode behaviorally relevant stimulus features - for example edge orientation or direction of movement - that are not explicitly encoded in the responses of individual afferents. Here we investigate the extent to which this process of elaboration of sensory representations occurs at an intermediate processing stage, namely the cuneate nucleus (CN). To this end, we record the response of CN neurons to stimuli that have been used to characterize responses both in the nerve and in the cortex, including skin indentations, vibrations, and scanned dot patterns. We then characterize the

response properties of CN neurons and compare them to their peripheral and cortical counterparts. We specifically gauge whether single neurons in CN receive convergent input from different cutaneous submodalities and assess how this input is integrated at that level. We then investigate whether CN responses are selective for higher order stimulus features, such as those encoded by cortical neurons. We find that that individual CN neurons exhibit properties that are indicative of convergent input from multiple cutaneous submodalities and perform computations that form the basis of those observed in cortex. We conclude that the CN is not a simple relay station for tactile information but rather is instrumental in its processing and elaboration.

Disclosures: A.K. Suresh: None. **A. Ayer:** None. **J.M. Rosenow:** None. **L.E. Miller:** None. **S.J. Bensmaia:** None.

Nanosymposium

722. Cortical and Subcortical Planning and Execution

Location: Room N227

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 722.04

Topic: E.04. Voluntary Movements

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1R01NS104834-01

Title: Sensorimotor control of complex tongue movement sequences in mouse

Authors: *D. XU[1], Y. CHEN[2], A. M. DELGADO[2], D. H. O'CONNOR[1];
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Abstract: A myriad of complex behaviors arise from tuning and sequencing basic motor patterns. Motor-induced sensory feedback is important for learning new sequences as well as altering existing sequences in response to a changing environment. To study the neural basis of sensorimotor sequence control, we developed a novel behavior in head-fixed mice where they learned to perform sequences of directed licks to drive a motorized lickport to reward locations. Tongue motions were captured by high-speed video and kinematics quantified by artificial deep neural nets. Contact forces between tongue and lickport were recorded by custom made sensors. Mice first learned two basic sequences within a week, in which they licked across seven angles within ~1 second. Later, unexpected lickport movements were randomly introduced to the basic sequences, causing the animals to miss the target. Experienced mice learned to change an ongoing sequence upon misses and make informed corrections to relocate the lickport. During behavior, we used silicon probes to record single-unit activity from various brain regions including tongue/jaw S1 (S1TJ, n = 234), tongue/jaw M1 (M1TJ, n = 127), anterior lateral motor cortex (ALM, n = 407) and other regions. Linear decoding of population activity showed that

neurons in S1TJ and M1TJ, but not ALM, strongly encoded instantaneous protrusion length and phase of the tongue within each lick cycle. Although S1TJ, M1TJ and ALM neurons all encoded tongue angles, S1TJ and M1TJ represented instantaneous angle whereas ALM represented the smoothly changing targeting angle. Being a higher order motor area, ALM, but not other regions, strongly encoded the identity of the sequence and instantaneous progress within a sequence (i.e. distance to goal). To examine the causal role of these brain areas in sequence control, we performed closed-loop optogenetic inhibition experiments (n = 4 mice) covering sequence initiation, mid-sequence and reward consumption periods. Bilateral inhibition of both S1TJ and ALM, but not control areas, impaired the control of ongoing tongue motions. In addition, ALM inhibition strongly impaired sequence initiation. Overall, our data show that S1TJ, M1TJ and ALM are important for the execution of tongue-based sensorimotor sequences and encode behavioral variables at different levels of abstraction.

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722. Cortical and Subcortical Planning and Execution

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Presentation Number: 722.05

Topic: E.04. Voluntary Movements

Support: NIH R01DE027236

Title: Decoding 3D tongue kinematics from population responses in sensorimotor cortex

Authors: *J. D. LAURENCE-CHASEN, K. BALASUBRAMANIAN, C. F. ROSS, N. G. HATSOPOULOS, F. I. ARCE-MCSHANE;
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Abstract: Dynamic tongue movements are crucial for chewing, swallowing, and speech. Mucosal mechanoreceptors and muscle spindles provide continuous sensory feedback that informs the tongue's rapid postural changes. The cortical basis of this vital sensorimotor behavior is still largely unknown because tongue kinematics has only been imprecisely measured, as 3-dimensional (3D) tongue kinematics cannot be visualized with traditional light or infrared videography. Here, we use an innovative method called XROMM (X-ray Reconstruction of Moving Morphology) to measure high-resolution 3D tongue kinematics while simultaneously recording from the orofacial sensorimotor cortex. Two Rhesus macaques (*Macaca mulatta*) were implanted with a lattice of tantalum beads in the tongue, and multielectrode arrays in the orofacial region of the primary motor and somatosensory cortices, along with floating microelectrode arrays in areas 3a and 3b. Tongue kinematics were captured at 200 Hz as the animals were chewing and swallowing fruit pieces, while ensemble neural

activity were simultaneously recorded. The neural recordings were mapped to the 3D Cartesian position of the tongue tip obtained during the behavioral task. Using a Kalman filter, we decoded 3D tongue kinematics from the activity of populations of cortical neurons. First, we show that it is possible to decode free-moving 3D tongue kinematics using orofacial neural ensembles. Second, we show that decoding performance improves significantly when the population comprised of neurons from both motor and sensory cortices, compared to the decoding performance with either one of them.

Disclosures: J.D. Laurence-Chasen: None. **N.G. Hatsopoulos:** None. **K. Balasubramanian:** None. **C.F. Ross:** None. **F.I. Arce-Mcshane:** None.

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Topic: E.04. Voluntary Movements

Support: R01DE027236

Title: Mixed encoding of sensorimotor information in orofacial cortical neurons

Authors: K. BALASUBRAMANIAN[1], J. LAURENCE-CHASEN[1], R. JUNOD[1], C. F. ROSS[1], N. G. HATSOPOULOS[1,2], *F. I. ARCE-MCSHANE[1];
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Abstract: The primary motor (MIo) and somatosensory (SIo) areas of the orofacial cortex are anatomically well-defined regions in the pre- and post-central gyrus, respectively. The neurons in these regions, nevertheless, are not distinctive in their encoding of sensorimotor information and show mixed motor- and sensory-related responses. To dissociate the cortical representations of touch and proprioception, we used an innovative sequence of nerve blocks to the sensory branches of the trigeminal nerve and delivered intracortical microstimulations (ICMS). Utah microelectrode arrays were implanted in MIo and SIo (areas 1 and 2) of two Rhesus macaques (*Macaca mulatta*), along with floating microelectrode arrays to access caudal MIo and areas 3a and 3b. Sub-threshold electrical stimuli (bi-phasic, 30 µA, 15 Hz) were delivered to individual recording channels while the animals were at resting behavior, under the conditions of with and without nerve-block. Subthreshold ICMS evoked muscle twitches while tactile inputs to the tongue and other oral structures were blocked through the nerve-block drug administration, allowing us to dissociate neurons with tactile-related responses from others with proprioception-related responses. Neurons that primarily carried tactile information also showed encoding of kinematics (i.e. position and velocity). Reciprocally, motor neurons showed additional encoding

of tactile information. Using a decoding framework to reconstruct movement kinematics, we found that the tactile neurons carried movement-related information as well. Such heterogeneity seen in MIo, areas 1 and 2 was largely absent in areas 3a and 3b. Neurons from areas 3a and 3b showed more homogeneous representation with neurons showing either pure tactile encoding or pure proprioceptive encoding.

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Nanosymposium

722. Cortical and Subcortical Planning and Execution

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Title: Sensorimotor integration for cued reaching movements through multiple bands of cortical oscillations from the motor and somatosensory cortices

Authors: *K. TAKAHASHI[1], H. WATANABE[2,1], M. MAKITANI[1], H. MUSHIAKE[2]; [1]Univ. of Chicago, Chicago, IL; [2]Tohoku Univ., Sendai, Japan

Abstract: Externally cued reaching tasks involve an orchestrated sensorimotor integration that takes place across many brain regions including the motor and somatosensory cortices each of which exhibits its own dynamical responses at different stages of reaching task. Various bands of cortical oscillations are involved in this sensorimotor integration process, but how each band in each area of the sensorimotor cortical areas is contributing to the process and how both areas interact over multiple oscillation bands remain largely unknown. Here, we implanted electrocorticogram (ECoG) grids into the primary motor cortex (M1) and the primary somatosensory cortex (S1) of a monkey and characterized oscillation dynamics through 1) peak phase locking timings to different behavioral events across multiple oscillation bands, α(10-12Hz), β (15~30 Hz) , and γ (40 - 200Hz) bands; and 2) coherence between M1 and S1 signals. The monkey was trained to use to make a reaching movement with one arm. The monkey kept the hand at the resting position for 2 seconds after a visual instruction target-cue randomly indicating one of the two positions (proximal or distal), then reached to the target after an

acoustic go-cue. Two 32-channel ECoG arrays (Matrix Array^{TM}, NeuroNexus, MI, US) were implanted in M1 and S1 each contralateral to the arm. The Percent of Phase Locking (PPL) of each oscillation band over trials was computed in relation to the instruction cue (IC) and movement onsets (MO) respectively. The amplitude of β transiently increased uniformly across both M1 and S1 briefly after IC, while before MO, there was an attenuation from rostral to caudal direction in M1 while S1 exhibited uniform attenuation. Both areas exhibited β rebound prior to the contact to the target, but more increase for the proximal targets. The peak PPL for β showed spatial clustering around MO, more in M1 for proximal target while more in S1 for distal target. The γband, especially around 70-80 Hz exhibited modulations around IC and after MO β attenuation both in M1 and S1. Coherence activity between M1 and S1 activities at IC was spatially homogeneous at β and γbands, while at MO β band showed spatial gradient from medial to lateral, while γband after MO showed more homogenous responses. Our findings indicate complex dynamics is present across multiple oscillation bands to characterize the sensorimotor integration between M1 and S1 for the reaching task.

Disclosures: **K. Takahashi:** A. Employment/Salary (full or part-time):; NeuroNexus. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NeuroNexus. **H. Watanabe:** None. **M. Makitani:** None. **H. Mushiake:** None.

Nanosymposium

722. Cortical and Subcortical Planning and Execution

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Topic: E.04. Voluntary Movements

Support: NIH R01 NS 082865

Title: Primary motor cortex does not exhibit orderly dynamics during grasp

Authors: ***J. M. GOODMAN**[1], A. K. SURESH[2], E. V. OKOROKOVA[2], N. G. HATSOPOULOS[1,2], S. J. BENSMAIA[1,2];
[1]Organismal Biol. and Anat., [2]Committee on Computat. Neurosci., Univ. of Chicago, Chicago, IL

Abstract: Rotational dynamics are observed in the population activity of primary motor cortex (M1) when monkeys make reaching movements, suggesting that M1 behaves like a pattern generator. In the present study, we examined whether similar dynamics are observed during grasping movements. To this end, we trained monkeys to grasp a variety of objects while recording time-varying hand kinematics and spiking activity from populations of M1 neurons. We then gauged the degree to which the population responses exhibited dynamics using a variety of standard analyses. We also investigated whether decoding of hand movements was improved

when the neuronal responses were smoothed with latent factor analysis via dynamical systems (LFADS), an approach that considerably boosts decoding of arm movements during reaching. We found that LFADS did not improve the decoding of hand movements during grasping. We conclude that M1 activity during grasping - in contrast to that during reaching - is not characterized by low-dimensional orderly dynamics.

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722. Cortical and Subcortical Planning and Execution

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Topic: E.04. Voluntary Movements

Support: German Research Foundation (DFG) SCHE 1575/1-1 & 3-1

Title: Behavior dependent states in segregated networks of low and beta synchronized neurons in the macaque fronto-parietal grasping circuit

Authors: *S. SHESHADRI, B. DANN, H. SCHERBERGER;
German Primate Ctr., Goettingen, Germany

Abstract: Oscillatory synchrony in distinct frequency bands is strongly related to different cognitive and behavioral processes. However, to understand the mechanisms underlying behavior dependent oscillatory synchrony, it is essential to study these processes at the level of their origin: single neurons. It is still unclear if the same or different neural populations participate in synchronization processes of different frequencies. Furthermore, to what extent are neurons synchronized within a frequency band for task conditions? To examine this, we trained two macaques to perform a delayed grasping task with randomly mixed instructed and free-choice trials in which a handle had to be grasped with one of two possible grip types. Neuronal activity was recorded in parallel from the fronto-parietal grasping network including the ventral premotor cortex (area F5) and the anterior intraparietal area (AIP) with 64 electrodes chronically implanted in each area. In each channel, we isolated single units and extracted local field potential (LFP) signals reflecting synchronized local population activity. Oscillatory synchronization between single neurons and larger neural populations in the network was quantified by the degree of phase locking between single units and LFPs using pairwise phase consistency (PPC). Since PPC is a rate independent measure of functional connectivity, it is suitable to compare functional network structure across conditions with different firing rates. We found significant functional connections in beta (17-35 Hz) and low (3-6 Hz) frequency bands, which varied antagonistically, with strong beta synchrony during steady epochs, i.e., fixation and

memory, and strong low frequency synchrony during the movement epoch. The beta and low frequency networks were composed of distinct groups of neurons resulting in independent networks of communication. Hub neurons were present in networks of both frequencies and maintained their hub status across conditions. Intriguingly, hub neurons contributed maximally towards network reconfiguration by modulating the strength of their functional LFP connections. Furthermore, the beta and low frequency networks were embedded in a low dimensional space within which the beta network reconfigured with grip type and task type, whereas the low frequency network reconfigured mainly with grip type. Together, we found distinct groups of beta and low frequency hub neurons that dominated condition-specific functional network reconfigurations. These dynamic functional network reconfigurations might provide a fundamental mechanism of flexible communication essential for cognitive and behavioral processes.

Disclosures: **S. Sheshadri:** A. Employment/Salary (full or part-time):; German Primate Center, Neurobiology Lab, Goettingen, Germany, Department of Biology and Psychology, University of Goettingen, Germany. **B. Dann:** A. Employment/Salary (full or part-time):; German Primate Center, Neurobiology lab, Goettingen, Germany. **H. Scherberger:** A. Employment/Salary (full or part-time):; German Primate Center, Neurobiology Lab, Goettingen, Germany, Department of Biology and Psychology, University of Goettingen, Germany.

Nanosymposium

722. Cortical and Subcortical Planning and Execution

Location: Room N227

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Presentation Number: 722.10

Topic: E.04. Voluntary Movements

Title: Neural population response dimensions identified with PCA contain mixed content and are only meaningful in case of high signal-to-noise ratio

Authors: *A. FILIPPOW[1,2], B. DANN[1], H. SCHERBERGER[1,2];
[1]German Primate Ctr. (DPZ), Goettingen, Germany; [2]Dept. of Biol. and Psychology, Univ. of Göttingen, Göttingen, Germany

Abstract: Recent technical developments allow the simultaneous recording of several hundreds of neurons, however in most studies the population response is of lower dimension than the number of recorded neurons. The most commonly used method for extracting the low-dimensional population response structure is principal component analysis (PCA). PCA is a deterministic method, yet, its application on neural activity requires proper evaluation, because neural activity is a sparse, non-negative and noisy point process and the number of recordable neurons is limited.
To evaluate the accuracy of PCA for characterizing the population response structure, we need to

know the ground truth structure of the underlying data. We therefore simulated neural population activity during a delayed center-out reach task. The population response was based on a low dimensional structure with a fixed set of orthogonal latent variables (LV). In agreement with previous studies, LVs were grouped into orthogonal subspaces for visual, preparatory or movement related activity. We simulated between 100 and 1000 neurons, each with random contributions from a fixed set of 9 - 15 LVs. The firing rates of simulated neurons, the amplitudes of LVs, and the distributions of neural contributions per LV were matched to the recorded neuronal populations.
PCA correctly identified the dimensions explaining most task-related variance. However, PCs were often mixtures of the true LVs. For example, two orthogonal LVs capturing visual and movement-related activity can mix into two PCs that capture variance related to both subspaces. This mixing depended on the difference in variances of the LVs, with LVs of similar variance mixing more readily. If the signal-to-noise ratio was low, PCs also mixed with noise in the same manner.
The distribution of explained variance per PC was more similar to a power law than the true distribution of explained variance per LV. If the signal-to-noise ratio was low, this distribution was smooth and continuous and without an apparent step at the number of true LVs.
In summary, PCA is a useful tool for dimensionality reduction. However, the distribution of explained variance per dimension is only conclusive about the true dimensionality, if the signal-to-noise ratio is sufficiently high. Our simulations confirm that PCs cannot be directly interpreted as LVs, and they provide a first scaffold to systematically evaluate the accuracy of population dimensions as identified by PCA. These results are highly relevant for correctly interpreting neural population data.

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Title: Recurrent neural network dynamics balance compression and expansion through learning

Authors: *M. S. FARRELL[1], S. RECANATESI[2], G. LAJOIE[4], E. T. SHEA-BROWN[3];
[1]Applied Mathematics, [2]Physiol. and Biophysics, [3]Univ. of Washington, Seattle, WA;
[4]Mathematics and Statistics, Univ. of Montreal, Montreal, QC, Canada

Abstract: Recordings of neural circuits in the brain reveal extraordinary dynamical richness and high variability. At the same time, dimensionality reduction techniques generally uncover low-dimensional structures underlying these dynamics when tasks are performed. In general, it is still an open question what determines the dimensionality of activity in neural circuits, and what the functional role of this dimensionality in task learning is. In this work we probe these issues using a recurrent artificial neural network (RNN) model trained by stochastic gradient descent (SGD) to discriminate inputs. The RNN family of models has recently shown promise in revealing principles behind brain function. Through simulations and mathematical analysis, we show how the dimensionality of RNN activity depends on the task parameters and evolves over time and over stages of learning.
We cast these findings in light of fundamental links between representation dimensionality and computation. Learning systems from the brain to deep neural networks often need to transform the dimensionality of their inputs: dimensionality expansion in order to distinguish different objects, and dimensionality compression in order to achieve solutions that generalize. In the neuroscience literature there is an emerging notion that the brain finds a minimal-dimensional solution: a solution that has high enough dimensionality to solve the task, but no more. This behavior has been attributed to multiple mechanisms, including mixed selectivity for higher-dimensional representations. We show that SGD is an effective mechanism for dimensionality compression, but may fail to expand dimensionality when this is required for success. In the context of RNNs, we find that dimensionality-expanding chaos is a mechanism that can help restore the balance. This work extends important findings on this beneficial role of chaos in networks with fixed recurrent weights in the computational neuroscience literature to the scenario where recurrent weights are modified through training. We find that in this scenario, the network can can balance the dimensionality compression induced by SGD and the dimensionality expansion properties of chaos to robustly find minimal-dimension solutions that solve the task and generalize well. We believe that this helps to explain why high variability is observed in neural circuits and how this variability paired with learning can naturally give rise to minimal-dimensional solutions.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Topic: H.01. Animal Cognition and Behavior

Support: HHMI
NS053415

Title: Two positive feedback loops induced by a neurotrophin at *Aplysia* sensorimotor synapses are important for the serial consolidation of learning-related facilitation produced by 5HT

Authors: *I. JIN, E. R. KANDEL, R. D. HAWKINS;
Neurosci., Columbia Univ., New York, NY

Abstract: ApNT (an Aplysia ortholog of mammalian BDNF) and its receptor, ApTrk, form two synaptic positive feedback loops that play important roles during the induction of intermediate-term facilitation (ITF) by 5HT at sensory neuron to motor neuron (SN-MN) synapses in isolated cell culture. We had earlier found that a presynaptic positive feedback loop mediated by the autocrine action of ApNT in the SN acts as the main driving force during the transition from short-term facilitation (STF) to ITF (Jin et al., 2018a). In turn, a trans-synaptic positive feedback loop mediated by the anterograde and retrograde actions of ApNT (Jin et al., 2018b) and the spontaneous release of glutamate (Jin et al., 2012a, b) orchestrates the induction of ITF by recruiting pre- and postsynaptic covalent mechanisms and activating protein synthesis in both neurons. Furthermore, protein synthesis in each compartment depends on mechanisms in the other compartment, so that the activated synapses act as one functional unit during the induction of ITF.

We report here that the major ApNT/ ApTrk signaling components of the two positive feedback loops are also essential during the induction of long-term facilitation (LTF): (1) overexpression of ApNT in the SN enhanced the amplitude of the basal eEPSP at 24-48 hr ($p < 0.05$); (2) injection of antisense oligos against ApTrk into the SN reduced facilitation of the basal eEPSP by 5 pulses of 5 HT at 24-48 hours, compared with sense oligo injection control ($p < 0.05$); (3) overexpression of ApNT in the MN increased the basal eEPSP at 24-48 hrs ($p < 0.01$); and (4) overexpression of a dominant negative construct of ApTrk in the MN reduced the facilitation produced by 5 pulses of 5 HT at 24-48 hours ($p < 0.05$).

These results are consistent with the idea that the two positive feedback loops that recruit pre- and postsynaptic covalent mechanisms and activate protein synthesis in both neurons during the induction of ITF continue to operate during the induction of LTF, resulting in the additional activation of transcription in the nucleus of the pre- and postsynaptic neurons necessary for LTF (Ghirardi et al., 1995; Hu et al., 2015). Specifically, the self-perpetuating ApNT positive feedback loop in the presynaptic neuron increases the levels of PKA and MAPK, which can then translocate into the nucleus to activate transcription via modulation of bZIP transcription factors such as CREB1, CREB2, and C/EBP (Jin et al., 2018 b; Martin et al., 1997). These results suggest that ApNT and ApTrk may play important roles at each sequential step of a serial consolidation process by recruiting covalent modifications during STF, translation during ITF, and transcription during LTF.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH K01 AG057833 (EG)
NIH-NIA Grant (ALH)

Title: *C. elegans* multisensory learning in simple T-mazes, as revealed by experiments and captured by mathematical models

Authors: B. SAKELARIS[1], K. ADIGA[1], A. GOETTEMOELLER[1], C. CHEH[2], V. BOOTH[1], A. HSU[1,2,3], ***E. GOURGOU**[1];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Natl. Yang Ming Univ. of Taiwan, Taipei, Taiwan; [3]Res. Ctr. for Healthy Aging and Inst. of New Drug Development, China Med. Univ., Taichung, Taiwan

Abstract: *C. elegans* ability to exhibit associative, non-associative and imprinted memory in the context of chemical stimuli is well established. Here we demonstrate that *C. elegans* nematodes are capable of spatial learning in a structured environment (maze). We employ 3D-printing technology to build a novel and versatile behavioral arena, the custom-made Worm-Maze platform. We show that *C. elegans* young adults can locate food in T-shaped mazes and, based on this experience, they can learn which maze arm to reach, after a single training session. Results indicate that learning is sufficient to introduce a strong bias in the decision-making process during navigation in the maze, even when in contrast with inherent preferences. We provide evidence that *C. elegans* food location ability in the maze requires tactile input, and that learning depends on chemosensation and mechanosensation. *C. elegans* learning in the maze shares certain properties with the working memory mechanism, especially regarding its short timeframe of retention and its sensitivity to distraction, i.e. environmental change. Moreover, it deteriorates with age earlier than food location ability decline, and preliminary results show that calorie restriction can enhance learning in older adults. In parallel with the experimental thrust, we develop a mathematical model to capture the dynamics of neuronal circuits that steer this behavior. The model suggests the presence of an interneuron responsible for sensory integration and explores two different scenarios for the learning mechanism. This is the first time that spatial learning is established and extensively characterized in *C. elegans*, and the underlying mechanism is broadly explored.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Topic: H.01. Animal Cognition and Behavior

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Title: A regulated molecular mechanism controls age-dependent memory decline

Authors: V. G. GHARAT, B. G. FENYVES, C. HAAB, A. ARNOLD, K. TISHINOV, F. PETER, D. DE QUERVAIN, A. PAPASOTIROPOULOS, ***A. STETAK**;
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Abstract: MinK-related peptides (MIRPs or KCNEs) are conserved transmembrane proteins that associate with voltage-gated pore forming potassium channels (K_v). In the brain, voltage-gated potassium channels play an important role in a multitude of neural functions including generation and regulation of LTP. However, the role of MIRPs in associative learning and memory, their regulation and possible role in age-dependent cognitive decline are currently unknown. Here we show that in *C. elegans* the KCNE homolog, *mps-2* is the sole member of the MiRP protein family that impairs long-term memory (LTAM) in young adult worms. Furthermore, we demonstrate that *mps-2* expression is up-regulated during LTAM, it is the major downstream target of the canonical CREB pathway and CRH-1/CREB directly bind to the promoter and regulates increase of *mps-2* expression during LTAM. MPS-2 finally modulates the activity of K_v2.1/KVS-3 and K_v2.2/KVS-4 ion-channel oligomers. Thus, our results suggest that the canonical CMK-1/CRH-1 pathway is regulating long-term memory predominantly through transcriptional regulation of *mps-2* levels, which in turn modulates activity of specific K_v potassium channels. On the other hand, baseline expression of *mps-2* decreases with age in a CREB independent manner and ectopic temporal induction of *mps-2* levels or use of exogenous promoter to drive *mps-2* at a constant level in aged worms inhibits age-dependent memory decline. Promoter mapping revealed that a repressor element is essential to control age-dependent expression and using Y1H we identified the transcription factor that is responsible for inhibition of *mps-2* expression. Finally, deletion of the transcription factor or the binding element inhibits down-regulation of *mps-2* expression and memory decline with age. Thus, the MPS-2/KVS-3/KVS-4 pathway may represent a novel molecular pathway essential for long-term memory, and involved in tightly controlling decline of memory during ageing.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

Location: Room S104

Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.04

Topic: H.01. Animal Cognition and Behavior

Support: R35NS097224

Title: Transient forgetting of aversive long-term memories in *Drosophila*

Authors: *J. M. SABANDAL, J. A. BERRY, R. L. DAVIS;
Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: Forgetting is a dynamic cognitive process crucial for the brain's memory management system. The counterbalanced forces of memory acquisition and consolidation versus forgetting guide animals to make flexible behavioral choices which are continuously enriched by experience. While a large bulk of literature in experimental psychology posits forgetting as a passive process, our recent findings illustrate that forgetting is also active. One form of active forgetting, termed intrinsic forgetting, involves a small cluster of protocerebral posterior lateral 1 dopamine neurons (PPL1 DAns) that slowly erode labile olfactory memories after learning but are vigorously removed when PPL1 DAn activity is elevated. However, information whether these forgetting cells cause memory failures for consolidated protein-synthesis dependent long-term memories (PSD-LTM) is missing. To probe whether active forgetting is involved in PSD-LTM we thermogenetically manipulated PPL1 DAn activity before retrieval and monitored the flies' performance. Blocking synaptic release from PPL1 DAns increased, while ectopic activation decreased the expression of PSD-LTM at 3 days. More specifically, the bidirectional activity of a single PPL1 DAn that innervates the upper stalk region of the mushroom bodies (MB), MBα2/α'2, produced the most robust differential expression of PSD-LTM. Surprisingly, waiting for several days after modulating PPL1 DA-MBα2/α'2 neuron activity allowed the expression of PSD-LTM to resurface, revealing the transient nature of the DAn-induced suppression or enhancement on memory expression up to 14 days. In addition, we discovered that the DA D5 receptor, damb, in the αβ MBns is required to mediate the DAn-induced suppression of PSD-LTM expression. Strikingly, exposing wild-type flies to either strong airflow or mild electric shock prior to retrieval dampened memory expression at 3 days by 50%. This plasticity was transient like PSD-LTM expression observed after DAn manipulation, persisting for less than 1 hour after the shock or strong airflow. Thus, we propose that these external perturbations on memory expression impinge on the DAergic circuit to trigger transient forgetting. These top-down, circuit-level observations offer an entrée to elucidate mechanisms for suppressors of retrieval as well as temporary blocks on memory. Collectively, our findings demonstrate that the influence of neural-genetic-environmental interplay shapes memory expression and may translate to memory loss in neurological and psychiatric disorders.

Disclosures: **J.M. Sabandal:** None. **J.A. Berry:** None. **R.L. Davis:** None.

Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Presentation Number: 723.05

Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH094607-05
5R21MH108929-02
NSF award No. 1453799

Title: Molecular motor Kif5C constrains synapse function and long-term memory by regulating synaptic translation

Authors: *S. SWARNKAR[1], Y. AVCHALUMOV[1], X.-A. LIU[2], B. RAVEENDRA[1], I. VILLANUEVA[1], S. MEDIOUNI[1], E. GRINMAN[1], S. VALENTE[1], K. MILLER[3], S. V. PUTHANVEETTIL[4];
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Abstract: Activity dependent changes in synaptic translation are a rate-limiting step for structural plasticity and memory storage. However, mechanisms regulating synaptic translation are not well understood. By assessing the necessity of two molecular motors Kif5C and KIf3A that are expressed in the same neurons and mediate active transport of gene products from the cell body, we studied the contribution of active transport in modulating structural plasticity. We find that shRNA mediated knocked down (KD) of Kif5C or Kif3A in primary hippocampal neurons resulted in decreased excitatory synaptic transmission, dendritic branching, spine density and morphology. Interestingly, unlike Kif3A increasing expression of Kif5C alone produced the opposite effect of KD phenotypes. We further find that unlike Kif3A, Kif5C is regulated by cAMP-PKA pathway and that Kif5C is a critical mediator of cAMP dependent changes in synapse function. Consistent with a role in regulating synaptic translation, we identified ~600 RNAs enriched in Kif5C complex. Kif5C KD reduced synaptic translation whereas its overexpression enhanced translation. We then assessed the significance of Kif5C in memory storage by sub-region specific manipulations and find that Kif5C KD in dorsal CA1 neurons of hippocampus decreased spatial memory and contextual fear memory whereas its overexpression enhanced spatial memory but did not affect contextual fear memory. Taken together these results establish that Kif5C is a key regulator of synapse function and long-term memory storage.

Disclosures: **S. Swarnkar:** None. **Y. Avchalumov:** None. **X. Liu:** None. **B. Raveendra:** None. **I. Villanueva:** None. **S. Mediouni:** None. **E. Grinman:** None. **S. Valente:** None. **K. Miller:** None. **S.V. Puthanveettil:** None.

Nanosymposium

723. Neural and Molecular Mechanisms of Memory

Location: Room S104

Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.06

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 AG058002-02

Title: Mef2 mediates cognitive enhancement and resilience in mice and humans

Authors: *S. BARKER;
MIT, Cambridge, MA

Abstract: Cognitive resilience (CR) describes a well-characterized phenomenon in which a subset of patients maintain healthy cognitive function despite harboring a large amount of brain pathology. CR has been documented in a wide range of neurological diseases including traumatic brain injury[1], and neurodegenerative disorders[2,3]. The molecular mechanisms that govern this neuroprotective state remain unknown, but individuals that exhibit resilience represent a unique source of insight into potential therapies that could preserve brain function in the face of disease. Here, we employ a two-pronged approach to dissecting the mechanism of CR. First, taking advantage of existing human brain transcriptomic data of control and Alzheimer's Disease (AD) patients, we identified individuals who maintained normal cognition despite having a large burden of AD pathology, i.e. those with high CR. We observed significant up-regulation of the MEF2 family of transcription factors (TFs) in resilient patients, when compared to patients whose cognition declined in response to neurodegeneration. Second, we utilized the only existing animal model of CR – environmental enrichment (EE) – to investigate the molecular mechanisms involved in the induction of CR. In both humans and rodent models of neurodegeneration, EE is one of the most robust resilience-promoting interventions[4,5]. We used ATAC- and nuclear RNA-sequencing to identify chromatin and transcriptional changes in cortical neurons of mice exposed to EE. Remarkably, genomic regions that became more accessible following EE were enriched for Mef2 binding sites. EE also directly increased levels of Mef2a expression and expression of putative Mef2 targets. Mef2 knockdown in the frontal cortex just prior to initiation of EE blocked improvements in cognition, demonstrating that Mef2 activity is necessary for environment-induced cognitive enhancement. Neurons lacking Mef2 showed hyperexcitability, which is one of the earliest features of Alzheimer's disease in both humans and mouse models. We demonstrate that EE in a mouse model of neurodegeneration leads to increased Mef2a expression and less neuronal hyperexcitability. Overall, our findings

reveal a novel and critical role for the MEF2 TFs in promoting cognitive health at baseline, and cognitive resilience in the context of neurodegeneration.

Disclosures: S. Barker: None.

Nanosymposium

723. Neural and Molecular Mechanisms of Memory

Location: Room S104

Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.07

Topic: H.01. Animal Cognition and Behavior

Title: Alternate biochemical pathways for enhanced cognition

Authors: *T. H. SANDERS;
Vanderbilt Univ., Nashville, TN

Abstract: Modulation of neural circuits has been shown to enhance learning and memory in rodents and humans. In this study, we examined two alternative manipulations previously reported to improve cognition: vagus nerve stimulation (VNS), and inhibition of histone deacetylase 2 (HDAC2). We have previously shown that cognition-enhancing VNS alters expression of histone modification and neuronal plasticity genes that play a prominent role in enhanced learning and memory. Here, we compare male Sprague-Dawley rats that received 30 minutes of intermittent VNS bursts on 4 consecutive days to those that received a single intracerebroventricular injection of HDAC2 anti-sense oligonucleotide (ASO). Both cohorts showed improved learning and memory, along with changes in cortical, hippocampal, and blood transcription profiles and epigenetic marks. Many of the significantly changed transcripts correlated with behavioral performance in a novel object recognition task. Interestingly, the chromatin modulation and gene expression changes differed dramatically between cohorts that received HDAC inhibitor injections versus those that received VNS. While HDAC2 ASO-treated rats showed behavioral and transcriptional changes associated with increased reward pathway activation, no such changes were observed in VNS-treated rats. Additionally, while HDAC2 rats displayed significantly reduced cortical and hippocampal HDAC2 along with primarily increased transcription of other genes, VNS induced changes that were more balanced between increased and decreased transcription with only small changes in HDAC2. However, VNS rats showed broader rearrangement of the epigenetic landscape as a whole. The overall changes observed in VNS-treated rats were more complex and included alterations in cholinergic, GABAergic, glutamatergic, serotonergic, immune, and endocrine pathways. Furthermore, examination of the cortex of VNS rats revealed significant increased expression of anti-viral and other miRNAs. Thus, although both rat cohorts showed improved novel object recognition and significant changes in plasticity, the observed brain circuit alterations were distinct. In conclusion, our

results demonstrate evidence that widely divergent transcriptome and epigenetic modulation profiles underlie alternate paths to enhanced learning and memory.

Disclosures: T.H. Sanders: None.

Nanosymposium

723. Neural and Molecular Mechanisms of Memory

Location: Room S104

Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.08

Topic: H.01. Animal Cognition and Behavior

Title: tPA-dependent behavioral brain mapping

Authors: *S. DOUCEAU[1], Y. HOMMET[2], L. LEBOUVIER[2], V. AGIN[1], D. VIVIEN[2,3]; [1]Normandie University, INSERM UMR-S U1237 Physiopathology and Imaging of Neurolog. Disorders, CAEN, France; [2]INSERM UMR-S U1237 Physiopathology and Imaging of Neurolog. Disorders, CAEN, France; [3]Caen-Normandie Univ. Hosp. (CHU), Dept. for Clin. Res., Caen, France

Abstract: Tissue plasminogen activator (tPA) is a serine protease expressed in the brain parenchyma, both during development and at adult stage, where it is expressed by different cell types including neurons and oligodendrocytes. Several studies have shown that tPA is expressed in key regions of the brain involved in the control of behaviors such as the dentate gyrus (DG) of the hippocampus and the basolateral nucleus (BLA) of the amygdala, with functions in the control of tasks such as spatial cognition and anxiety. Accordingly, behavioral tasks performed in constitutive tPA-deficient (tPA-null) mice have confirmed spatial memory deficits (Barnes maze), a locomotor hyperactivity (open-field) and an anxiolytic phenotype (O-maze and open-field) relative to control mice. In this model, no information about brain structure-dependent phenotypes nor lifespan-dependent effects has been provided. To address this question, we generated tPA floxed mice allowing conditional tPA deletion (cKO) following stereotaxic injections of adeno-associated virus driving cre-recombinase expression (AAV9-CBA-Cre-GFP). Using this approach, we first investigated whether tPA expressed in the DG could contribute to the phenotypes observed in tPA-null mice. Our results show that DG-tPA cKO mice exhibited a locomotor hyperactivity in the open-field and spatial memory deficits in the Barnes maze. However the anxiety state tested in the O-maze and the open-field was similar in DG-tPAcKO mice and control mice. We then assessed whether tPA expressed in the BLA could play a role in the regulation of anxiety. We did not observed change in the anxiety state between BLA-tPAcKO mice and control mice suggesting that amygdalian tPA is not involved in the regulation of trait-anxiety at the adult stage. Altogether our results show that tPA expressed in DG neurons regulates locomotor activity and spatial memory. Investigations of the role of tPA in other brain

areas are ongoing, including the prefrontal cortex containing tPA expressing neurons, a structure also described to play a role in the regulation of trait-anxiety.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Presentation Number: 723.09

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 DA042057 02
DoD W81XWH-13-1-0377

Title: Repeated variable stress exposure in mid-adolescence attenuates behavioral, noradrenergic and epigenetic effects of trauma-like stress in adult male rats

Authors: *L. E. CHABY[1], N. SADIK[1], N. BURSON[1], S. LLOYD[1], K. O'DONNEL[1], J. J. WINTERS[2], C. V. CHEN[3], I. LIBERZON[4], S. A. PERRINE[1];
[1]Wayne State Univ., Detroit, MI; [2]Univ. of Michigan, Ann Arbor, MI; [3]Texas A&M Univ., Bryan, TX; [4]Psychiatry, Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Stressful experiences in adolescence can regulate vulnerability to trauma and psychopathology in adulthood through lasting brain-regions specific changes in neurochemical pathways, including neurotransmitter and epigenetic modifications. Feedforward effects of adolescent stress can impair health and social well-being, yet conflicting literature describes a capacity for adolescent stress to promote risk or resilience to adverse effects of subsequent stress exposure on cognition. We investigated the effects of repeated stress in adolescence on vulnerability to adverse cognitive, epigenetic, and norepinephrine (NE) changes following traumatic stress in adulthood. To do this, we exposed male rats to repeated variable stress exposure in mid-adolescence (33-35 days old), then tested a cognitive deficit of trauma-like stress (single-prolonged stress) in early adulthood (58-60 days old). We then evaluated brain regions mediating fear learning for NE and histone deacetylase (HDAC) 4 and 5 levels; the latter is linked to long-term memory formation and vulnerability to posttraumatic stress disorder (PTSD). We found that trauma-like stress exposure in adulthood, in the absence of adolescent stress, induced an extinction retention deficit, characteristic of PTSD. However, this cognitive deficit was eliminated by apparent preparatory effects of prior adolescent stress. Changes in HDAC levels in brain regions mediating fear learning were consistent with this pattern; only animals exposed to adult trauma-like stress in the absence of adolescent stress showed reduced HDAC4 and HDAC5 in the hippocampus, infralimbic cortex, and prelimbic cortex (PL), but not

in the amygdala, suggesting that adolescent stress exposure regulates the epigenetic effects of subsequent stress in adulthood with regional-specificity. Adolescent stress also regulated effects of adult trauma-like stress on NE with regional-specificity. Exposure to adult trauma-like stress decreased NE levels in the hippocampus, but this effect was mitigated at a trend level by adolescent stress exposure. Conversely, PL NE levels were elevated by the combination of adolescent stress and adult trauma-like stress, but were not affected by adult trauma-like stress alone. Thus, repeated stress in adolescence has diffuse, region-specific programmatic effects on epigenetic and neurotransmitter responsivity to traumatic stress in adulthood, and can buffer adverse cognitive effects of trauma-like stress. Our results highlight the need for more comprehensive understanding of the lasting effects of adolescent experiences on class IIa HDAC expression and noradrenergic signaling.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.10

Topic: H.01. Animal Cognition and Behavior

Support: NINDS Grant 5R01NS021229-34

Title: Fear conditioning strengthens the mouse dorsal CA1 commissural pathway *in vivo*

Authors: *M. SUBRAMANIYAN[1], S. MANIVANNAN[1], V. CHELUR[2], T. TSETSENIS[1], J. A. DANI[1];
[1]Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [2]Columbia Univ., New York, NY

Abstract: The hippocampus is essential for spatial learning and memory, which can be readily assessed by a contextual fear-conditioning task, where animals learn to associate a place with aversive events like foot shocks. Although several studies have revealed cellular and molecular level changes in the hippocampus associated with this task, direct evidence of learning-related synaptic strength change occurring in vivo is still lacking. To address this, we applied local field potential recording combined with motion tracking in awake behaving mice (~3.3 months old). A stimulating electrode was placed in the left dorsal CA1 region and recording tetrodes were placed in the right dorsal CA1 region. Synaptic strength in the commissural pathway was monitored by quantifying the field-EPSP response for 2 hours before and 3 hours immediately after fear conditioning (2 min exploration of conditioning chamber, followed by 5 foot shocks (0.6mA, 1sec duration) with a 30 sec time interval after each shock). Relative to baseline, after

fear learning, we observed an overall increase in synaptic strength (n = 24 mice). In addition, the animals spent more time (median: 16%, range: 0-56%) in sleep state in the post-shock recording period than in the pre-shock period (median: 0%, range: 0-19%), even though the experiment was done during their active phase of daily cycle. Surprisingly, relative to awake periods, in non-rapid eye movement (non-REM) sleep, the synaptic strength was significantly higher in both pre- and post-shock recording periods. To avoid sleep-related changes confounding with learning-related changes, we removed sleep segments from all datasets in the study and still found a significant enhancement of synaptic strength in the post-learning period relative to the baseline. No significant change was found in the no-shock control condition (n = 10) where the animals went through the same above training procedure but with no foot shocks, indicating that spatial exploration of novel place did not result in a noticeable synaptic strength change. When the shock intensity was reduced to 0.4mA in the fear conditioning procedure (n = 11), no significant change in the synaptic strength was found, indicating that the synaptic potentiation was below detectable level at this shock intensity. These results suggest that the synaptic strength of the commissural pathway of dorsal CA1 region undergoes potentiation in vivo due to contextual fear conditioning.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

Location: Room S104

Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.11

Topic: H.01. Animal Cognition and Behavior

Support: NSFC 31471076

Title: Hippocampal neurons integrating past memory and present context for subsequent action

Authors: *C. YANG[1,2], Y. NAYA[1,3,4];
[1]Ctr. for Life Sci., [2]Acad. for Advanced Interdisciplinary Studies, [3]Sch. of Psychological and Cognitive Sci., [4]IDG/McGovern Inst. for Brain Res. at Peking Univ., Peking Univ., Beijing, China

Abstract: The declarative memory system equips us to remember the information of past experiences or knowledge so as to use the acquired information flexibly for subsequent action. Importantly, while numerous studies have demonstrated involvements of the medial temporal lobe (MTL) in the formation and retrieval of declarative memory, it is largely unknown how MTL neurons process the retrieved information when we use it in a given context. To address this problem, we previously devised a memory task for non-human primate, in which

recollection of the item-location association and its usage were separated in a single trial, and demonstrated a double dissociation of the recollection of past knowledge and its usage between PRC and HPC (Yang et al., SfN 2018). In the present study, we investigated how HPC neurons transformed the retrieved knowledge into the goal-directed information according to the incoming perceptual context. In the memory task, two sets of four visual items were used as item-cue stimuli. Each item-cue stimulus was associated with one particular location out of four relative to a context-cue stimulus. In each trial, an item-cue and a context-cue were sequentially presented with a delay in-between. The monkeys were required to saccade to the target location in accordance with a combination of the two cues. A total of 456 HPC neurons were recorded from two macaques and 66 neurons exhibited significant co-location-selective activities ($P < 0.01$) that reflected retrieved location information during the context-cue presentation and the following delay period. Population analysis showed that the incoming context signal was converged with the retrieved signal in an additive way, and the effect was significant ($P < 0.01$) from 228 to 458 ms after the context-cue onset. Following the additive convergence of the memory and perceptual signals, HPC exhibited two types of target selectivity in a sequential manner. Population-averaged time course for 72 target-selective HPC neurons reflected the mental location of item cues entering into the preferred locations of individual target-selective neurons from 309 to 786 ms after the context-cue onset ($P < 0.01$) and finally represented the target location itself regardless of the first retrieved location from the item-cue. The error analysis for the target-selective activity suggested that the animals' subsequent choice was predicted by the target signal in HPC ($P < 0.0005$, Wilcoxon's signed-rank test). These results suggest that HPC neurons constructs a goal-directed information by combining memory and current perception signals, which influence subsequent animals' actions.

Disclosures: C. Yang: None. **Y. Naya:** None.

Nanosymposium

723. Neural and Molecular Mechanisms of Memory

Location: Room S104

Time: Wednesday, October 23, 2019, 1:00 PM - 4:15 PM

Presentation Number: 723.12

Topic: H.01. Animal Cognition and Behavior

Title: Spatial novelty enhances flexible learning through ventral hippocampal-prefrontal metaplasticity

Authors: *A. J. PARK[1], K. MARTYNIUK[1], C.-Y. CHANG[1], A. I. ABBAS[2], C. KELLENDONK[3], A. HARRIS[1], J. GOGOS[1], J. A. GORDON[4];
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Abstract: Modifying established behavior in novel situations is essential for everyday life, and patients with psychiatric disorders often lack this flexibility. Previous studies, however, focused on how novelty boosts memory retention via the dorsal hippocampus (dHPC). Strong baseline brain connectivity impairs flexible learning. Novelty, by contrast, induces metaplasticity in which low frequency activity weakens established synaptic connections to allow further plasticity. To explore whether novelty enhances flexible learning by reducing existing circuit connectivity and thereby opening a plasticity window, we used at least 7 mice per group and conducted data analyses blind to the groups. Simultaneous recordings were performed from novelty-responsive areas the dHPC, ventral HPC (vHPC), ventral tegmental area (VTA), and medial prefrontal cortex (mPFC). To establish a behavioral bias, 4-month-old male and female C57BL/6J mice ran 3-day-free-run sessions getting reward in a T-maze and developed an arm preference. The following day, mice were exposed to either a novel or familiar arena and trained on a delayed-non-match-to-sample T-maze task 1 hour later. We find that novelty enhances learning to overcome established arm bias, especially when the goal arm is not the preferred arm. Compared with familiar conditions, novelty entrains the vHPC to local low frequency theta (4-12 Hz) activity and weakens vHPC-mPFC connectivity, which was measured by vHPC activity-evoked mPFC spikes and mPFC unit phase-locking to vHPC theta oscillations. These novelty effects last at least for 1 hour until the onset of T-maze training. Information theory analyses revealed that mPFC cells encode task-relevant information as the weakened vHPC-mPFC connectivity strengthens through training. Conversely, in familiar conditions, vHPC-mPFC connectivity remains stable and mPFC cells do not update information content, indicating that novelty weakens pre-training connectivity allowing training-induced plasticity to occur. Moreover, the VTA provides dense dopaminergic inputs to the vHPC, but not the dHPC, and novelty-induced VTA theta oscillations entrain vHPC theta activity. Finally, infusing the dopamine D1-receptor inhibitor SCH23390 or optogenetically inhibiting D1-expressing novelty-responsive cells in the vHPC abolishes the novelty effects. Thus, novelty enhances flexible learning via metaplasticity within vHPC-mPFC circuitry, a process mediated by D1-receptor-dependent low frequency vHPC activity. As pathologic vHPC-mPFC connectivity is prominent in many psychiatric disorders, our study provides new mechanistic insight for therapeutic interventions.

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Nanosymposium

723. Neural and Molecular Mechanisms of Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH 5R01MH106617
NARSAD / BBRF

Title: Dynamics of prefrontal cortex assemblies activation associated with contextual fear discrimination learning

Authors: *J. MAYER, J. PASTORE, J. H. SPEIGEL, III, T. W. BAILEY, **E. KORZUS**; Dept. of Psychology & Neurosci. Program, Univ. of California Riverside, Riverside, CA

Abstract: Recent studies have revealed molecular and synaptic mechanisms of information storage and it has been postulated that a neural representation, referred to as assembly, activated during memory encoding is preferentially recruited during memory retrieval. How specific neuronal representations are recruited to form and maintain memories is unknown. Present studies aim at identifying assemblies relevant to contextual fear modulation and assess circuit dynamics underlying disambiguating safety and danger. Fear behavior is regulated by the medial prefrontal cortex (mPFC) via fear excitation and inhibition mechanisms involving inter- and intra-regions interactions across larger hippocampal-prefrontal-amygdala networks. Current research investigates how the mPFC is able control fear responses under the hypothesis that accuracy of fear memory is attained via reduction of fear responses to non-reinforced stimuli. Alterations of prefrontal network dynamics during context-dependent fear discrimination learning is evaluated via real-time network activity assessment in the prelimbic subdivision (PL) of the mPFC using miniaturized head-mounted microscopes followed by computational analysis of large-scale neuronal network patterns. These miniaturized microscopes are capable of measuring calcium transients reflecting neuronal activity from more than a thousand neurons in a freely behaving mouse. To evaluate learning triggered neuronal network state shifts, real-time prefrontal network activity is recorded in response to dangerous (CS+) and safe (CS-) context stimuli across all behavioral testing stages of differential fear conditioning (DFC) to uncover the neural mechanisms underlying learning to distinguish between danger and safety. The PL network exhibited discrete network state shifts associated with fear discrimination learning which were not present in the PL-targeted genetic mutant mice showing abnormal learning on DFC task. Global dynamics of coactive neuronal subsets constituted after fear conditioning and unfolded elevated network activity patterns during recognition of the contexts with strongest changes during presentation to CS-, the previously generalized but safe context. Assemblies' detection and their activity pattern analysis revealed the development of assembly activity bias towards CS-. These finding were supported by a graph theoretical approach towards sequence analysis of assembly activation patterns. Understanding how fear memories are encoded and kept resistant to confusion is clinically relevant as fear memory over-generalization is a hallmark of phobias, PTSD and generalized anxiety disorder.

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Nanosymposium

724. Human Executive Functioning

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Presentation Number: 724.01

Topic: H.02. Human Cognition and Behavior

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the Fundamental Research Funds for the Central Universities (2017EYT33)
the Thousand Young Talents Program of China

Title: Dissociating neural networks of metacognition from attention driven by decision uncertainty

Authors: *L. QIU, J. SU, X. WAN;
State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal University, IDG/MacGovern Inst. for Brain Res., Beijing, China

Abstract: Metacognition is a meta-level cognitive control used to monitor and control object-level cognitive processes. Metacognition accompanies decision-making with decision uncertainty. Decision uncertainty is a self-evaluated belief about the degree that the choice is not correct. When the decision uncertainty is high, the process of metacognitive control should be more stimulated to revise the previous decision, in turn, reduction of the decision uncertainty, if allowed to make the decision again. However, decision uncertainty may also increase attention during the redecision phase, to allocate more cognitive resources. Critically, the metacognition neural network and the attention network are commonly in the frontoparietal control network. Thereby, it is so far unknown whether metacognition and attention are commonly involved in the same neural network, or they are distinct. In this study, we set out to distinguish the metacognition network from the attention network using functional magnetic resonance imaging and transcranial magnetic stimulation (TMS). Eighteen participants made two sequential decisions in each trial. There were three different combination conditions: (1) hard-hard; (2) control-easy and (3) control-control. Hard trials caused decision uncertainty, while easy and control would not. The decision uncertainty was measured by the participants' confidence ratings on their decisions. Hence, Hard trials would cause both metacognition and attention, while easy trials would only cause attention. Our results showed that two distinct neural networks in the frontoparietal areas: metacognition (hard - easy trials) and attention (easy - control trials) during the decision2 phase, although both sharing similar areas in the cingulate and parietal cortices; Further, the functional connectivity analyses also showed the two networks were distinct. The psychophysiological interaction analysis suggested that the metacognition and attention network had a hierarchic organization, the metacognition network modulated the attention network, and the attention network modulated the visual system. To further illustrate the differential casual effects of two networks, we employed online TMS protocol (2 HZ) to interference the metacognition and attention regions in the parietal cortex. TMS on the attention region delayed

the response times in the two decisions, while TMS on the metacognition region only delayed the response times in the decision2. Taken together, our findings revealed that the metacognition network should be distinct from the attention network, although both might be involved in the cognitive control processes.

Disclosures: L. Qiu: None. **J. Su:** None. **X. Wan:** None.

Nanosymposium

724. Human Executive Functioning

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Topic: H.02. Human Cognition and Behavior

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Title: Unbalance between proactive and reactive control of intrusive memory in post-traumatic stress disorder

Authors: *G. LEONE[1], A. MARY[1], J. DAYAN[1], C. POSTEL[1], F. FRAISSE[1], T. VALLÉE[1], V. DE LA SAYETTE[1], D. PESCHANSKI[2], F. EUSTACHE[1], P. GAGNEPAIN[1];
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Abstract: Introduction
When confronted with unwelcomed memories, the human brain is gifted with the ability to suppress memory traces using inhibitory control, resulting in a long-term forgetting. Theories of PTSD, however, implicate proactive avoidance and suppression of traumatic memories as increasing intrusive memories. Here, we tested whether this paradox may result from a compromised control system in PTSD, disrupting the balance between proactive and reactive countermanding of unbidden intrusive memories.
Methods
We recorded brain activity using fMRI while 54 participants with full or partial PTSD from the Paris attack of 13th November 2015 (EX+; 25M, 36.8y), 46 trauma-exposed control participants without PTSD (EX-; 27M, 35.8y), and 70 healthy non-exposed subjects (NE; 35M, 33y), attempt to suppress unwanted memories of previously learnt word-objects pairs. Keeping track of the temporal pattern of memory intrusion self-reported by participants, we computed the subjects' trial-by-trial intrusion expectations (EXP) and prediction errors (PE) using a Bayesian model (two-level Hierarchical Gaussian Filter). We then explored using DCM how EXP and PE signals

influenced the effective connectivity between the right anterior/posterior MFG, two core nodes of the inhibitory control system, and memory target regions, including the rostral and caudal hippocampus.

Results

The aMFG is preferentially mediating the reactive control of PE by downregulating the cHIP in NE (M= -0.18, 95% CI = [-0.26, -0.04], p <.05) and EX- (M= -0.23, 95% CI = [-0.45, -0.05], p<.05) participants. This capacity was not seen in EX+ (M= 0.02, 95% CI = [-0.13, 0.19], p = .76) and disrupted compared to both NE and EX- (p<.05). On the contrary, EX+ showed greater pMFG-mediated proactive downregulation of the rHIP based on EXP signal (M= -0.49, 95% CI = [-0.63, -0.27], p <.05) when compared to NE (M= -0.19, 95% CI = [-0.43, -0.16], p=.07) and EX- (M= -0.26, 95% CI = [-0.28, -0.05], p<.05).

Discussion

We found an unbalance in favour of proactive control in PTSD, who failed to reactively suppress the counter-intentional recollection of artificially created intrusive memories. Our findings shed light on a novel therapeutic target for PTSD that should aim to disrupt the over-engagement of proactive avoidance based on beliefs, and promote reactive suppression of intrusion signal.

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Nanosymposium

724. Human Executive Functioning

Location: Room S401

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 724.03

Topic: H.02. Human Cognition and Behavior

Title: Anterior prefrontal cortex conveys feature information of novel stimuli during unconscious reallocation of attention

Authors: *L. GÜLDENER[1], A. JÜLLIG[1], D. SOTO[2], S. POLLMANN[1,3];
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Abstract: Adapting to novelty is essential for an organism's survival in an uncertain world. Visual attention thus evolved as adaptive control mechanism allowing humans to switch between "exploitative" and "exploratory" processing modes. These enable the sustained pursuit of a successful strategy, or the evaluation of new strategies that seem more beneficial in a given situation. Neuroimaging evidence consistently links the anterior prefrontal cortex (aPFC) to exploratory attentional control underscoring the importance of aFPC for the ability to rapidly

respond to environmental changes. Such changes may be complex and occur very rapidly. Yet, it is currently unknown if this attentional role of the aPFC necessitates awareness. Here we hypothesised that the aPFC serves a role in attentional reallocation in the full absence of conscious awareness. Fourteen volunteers participated in an fMRI study using a discrimination task in which they had to distinguish between varying orientations of a briefly presented and masked grating stimulus. Combining signal detection theory and subjective measures of awareness, we show that behavioral performance on unaware trials is consistent with visual attention being weighted towards repeated orientations and reallocated in response to a novel unconscious orientation. Whole brain group level univariate analysis of fMRI data revealed a network of brain areas including occipital, parietal, dorsolateral, and anterior prefrontal cortex (aPFC) to be specifically sensitive to unaware changes in the stimulus orientation. Importantly, using classification searchlight analysis, we found that unaware orientation information of the novel stimulus could be decoded from BOLD activity patterns of those regions up to the right aPFC. The results support the current view on the functional role of aPFC to serve the exploratory reallocation of attention, as we show aPFC signalling in a situation that requires the change of the current attentional weighting. Importantly, the role of the aPFC in attentional reallocation was observed in the full absence of conscious visual awareness. This result has theoretical implications for understanding the distinction between attention and consciousness by indicating that both can be dissociated. More critically, the present results are in keeping with emerging evidence that higher-order cognitive control mechanisms can be deployed without conscious awareness. Information regarding unconscious stimulus changes can be represented across a network of brain regions up to the aPFC contradicting the traditional view that unconscious information processing is modular, domain-specific and transient.

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Nanosymposium

724. Human Executive Functioning

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Presentation Number: 724.04

Topic: H.02. Human Cognition and Behavior

Title: Effectiveness of 4 × 1 multielectrode tDCS on influencing executive control during mind wandering

Authors: *N. M. BOAYUE, G. CSIFCSÁK, I. V. KREIS, J. M. GROOT, I. C. FINN, A. E. VOLLSUND, M. MITTNER;
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Abstract: There is consensus on the involvement of executive functions (EF) in mind wandering (MW). However, there are divergent views on the exact nature of the EF-MW relationship. One

view, the “Executive use (EFu)” view postulates that MW consumes the same executive resources as the ongoing task at hand such that EF can flexibly be allocated to either process. On the other hand, the “Executive failure (EFf)” hypothesis posits that MW is the outcome of the failure in executive control to keep focused on the primary task. In this preregistered study, we investigated if a 4 × 1 multielectrode transcranial direct current stimulation protocol targeting the left dorsolateral prefrontal cortex modulated EF performance, behavioral variability and self-reported MW in a novel behavioral task. The study was designed to produce opposite predictions for the EFu and EFf hypotheses such that each of the views (or none) can be supported by the data, provided that active 4 × 1 multielectrode tDCS influences either EF, MW, or both. Our task required the subjects to respond with random left-right finger-tapping sequences in rhythm with a fast, ongoing metronome. EF performance was measured by the degree of randomness in the finger-tapping sequences(approximate entropy, AE), whereas behavioral variability (BV) was quantified as the standard deviation of the inter-tap-intervals (i.e., the time between subsequent finger-taps). In a double-blind, sham-controlled, between-subject design, participants were randomized to one of the 2 experimental groups (active vs. sham tDCS, N=30 in each). We found that relative to being on-task, MW was associated with larger BV and lower AE, but there was no significant effect of stimulation on any of the global measures that we predicted in our preregistered analyses. However, exploratory analyses using a more fine-grained analysis based on single-probe data using ordinal probit-regression models showed evidence that brain-stimulation may have reduced MW. This finding is in contrast to earlier studies finding an increase rather than a decrease of MW using a bipolar montage (Axelrod et al., 2015, 2018). Because of the ineffectiveness of the 4 × 1 multielectrode tDCS to affect EF based on our preregistered analyses, our results regarding the EFu and EFf hypotheses were inconclusive. However, we show that off-task responses can be predicted above chance-level using online measures of entropy and behavioral variability.
Open Science Framework (OSF) preregistration: https://osf.io/4hvd

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Title: Fmri adaptation vs pattern analysis: Evaluating methods for measuring human PFC representational geometry and dimensionality

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Abstract: The human prefrontal cortex (PFC) is necessary for the expression of flexible behavior and the activity of its neurons is known to code a variety of task variables. However, PFC representational geometry and its relationship to flexibility remain poorly understood. An important property of this geometry is dimensionality. High-dimensional representations of task variables may support flexibility in a neural network by providing a basis set for implementing rapid transitions between different task states. In highly trained macaques, lateral PFC representations of task variables approach maximum dimensionality and predict success on the task. In humans, the measurement of PFC representational geometry has been hampered by the relatively low reliability of fMRI BOLD activity patterns and the difficulty of decoding their information content. fMRI adaptation can potentially circumvent these problems by leveraging neuron-level repetition suppression to recover geometry and estimate dimensionality. Here we systematically evaluate fMRI adaptation and multi-voxel pattern analysis (MVPA) methods for their efficacy in providing reliable estimates of representational geometry and dimensionality across different regions of the brain. Participants were asked to solve a 3-dimensional, audio-visual parity classification task over five fMRI sessions. Leveraging a large amount of within-participant data, we estimated all pair-wise multi-voxel pattern distances and pair-wise repetition suppression effects in parcels across the brain. Additionally, we estimated representational dimensionality in each parcel using both multi-voxel pattern distances and repetition suppression effects. We report the reliability and cross-method correspondence of these two approaches to studying representational geometry in PFC and other regions across the human brain.

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Topic: H.02. Human Cognition and Behavior

Support: Fondecyt 1180932

Anillo ACT1414

Title: Non-linear modulation EEG complexity by different degrees of propofol sedation and its relation to responsiveness

Authors: *G. BONCOMPTE, V. MEDEL, T. OSSANDON;
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Abstract: Anesthesia is essential for a great number of critical medical procedures. Different anesthetics produce diverse changes in electroencephalographic (EEG) activity, but they all share the common effect of changing the patient's state of consciousness (SC) to unresponsive unconsciousness. The mechanisms underlying this convergence have remained elusive for decades. SCs can be characterized by the quality and diversity of the phenomenological experiences they can support, and their related patterns of brain activity; regular wakefulness support a much broader spectrum of possible experiences than unresponsive unconsciousness. In this line, recent work has attempted to characterize different SC using the complexity of brain activity during different SC. Lempel-Ziv complexity (LZc) of the EEG signal has been used to this effect. Lower complexity valued have been reported for deeply anesthetized than for wakeful SC, which suggests that anesthetics linearly reduce the complexity of brain activity. Here we show that under intermediate doses of propofol, EEG complexity is significantly greater than for baseline condition. Also, inter-trial variability of LZc strongly increases in sedation compared to baseline. We also compared the relation of LZc with subject's responsiveness during a simple discrimination task, an indicator of their SC. We found a strong positive correlation between LZc and performance, more pronounced than the propofol blood concentration - performance correlation. No correlation was found between propofol level and LZc. This indicates that, for propofol, LZc is a better predictor of responsiveness, and thus of SC, than the blood concentration of anesthetic. Analyzing the topological distribution of these changes in LZc, we found the main differences between sedation levels in fronto-central electrodes. However, electrodes that best distinguished moderate sedation with low-performance from the baseline condition where located in left and right parietal areas. We found differential influences of spectral changes to the signal towards LZc. Differences between conditions were basically unchanged when delta-theta frequencies were abolished. However LZc values strongly decreased and ceased to distinguish between sedation levels when beta-gamma frequencies where filtered out. Our results 1) suggest that the transition from wakefulness to deep anesthesia is not linear or monotonic, 2) highlight LZc as a possible candidate for measuring states and transitions between SC in clinical contexts and 3) characterize the topological distribution and frequency-dependency of LZc under moderate propofol sedation.

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Nanosymposium

724. Human Executive Functioning

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Presentation Number: 724.07

Topic: H.02. Human Cognition and Behavior

Support: UK Medical Research Council Grant to MCA: MC-A060-5PR00

Title: Inhibitory control of actions and memories: Common control processes, dissociable targets

Authors: *D. APŠVALKA[1], T. W. SCHMITZ[3], C. S. FERREIRA[4], Y. GUO[5], J. B. ROWE[2], M. C. ANDERSON[1];
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Abstract: Being able to control unwanted motor actions and memories is essential to healthy functioning and well-being. Prior research suggests that the ability to inhibit prepotent responses generalises across different domains, including motor and memory processes, and is supported by common brain mechanisms. There is an overall agreement that the prefrontal cortex (PFC) is critically involved in inhibitory control. Some disagreement exists, however, which subregions of the PFC are central to the inhibitory processes, and whether these subregions are domain-general or domain-specific.

We examined in the same individuals the potential domain-general mechanisms of inhibitory control of actions and memories. During an fMRI session, participants (N = 24) performed intermixed blocks of motor stopping (Stop-Signal) and memory suppression (Think/No-Think) tasks. We found that the efficiency in stopping motor actions was related to the efficiency in suppressing memories (r = .600, 95% CI: .268 to .797), suggesting a common inhibitory process. Critically, motor and memory inhibition evoked conjoint activations in the right dorsolateral (DLPFC) and ventrolateral (VLPFC) PFC regions. These supramodal regions were corroborated in an independent meta-analytic conjunction analysis of between-subject motor stopping and memory suppression studies. Moreover, DLPFC and VLPFC were bi-directionally coupled during the two inhibitory tasks and functionally related to the efficiency to stop actions and memories. Nevertheless, the shared DLPFC and VLPFC control regions selectively coupled with motor cortex or the hippocampus, depending on the process being stopped, and produced domain specific down-regulation of activity in these regions. This indicates that the domain-general nature of inhibitory control is achieved by the dynamic modulation of the domain-specific target regions.

Our findings support the existence of a domain-general mechanism involved in stopping actions and memories and provide strong evidence that both DLPFC and VLPFC are central to the domain-general inhibitory control. The supramodal control regions in the PFC promote down-regulation of domain-specific target areas, depending on the nature of the content being stopped: motor cortex for stopping actions and the hippocampus for stopping memory retrieval.

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Nanosymposium

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 102201
NSF Grant CAREER 1752355

Title: β-burst events reveal the trial-to-trial dynamics of movement initiation and -inhibition

Authors: *J. R. WESSEL;
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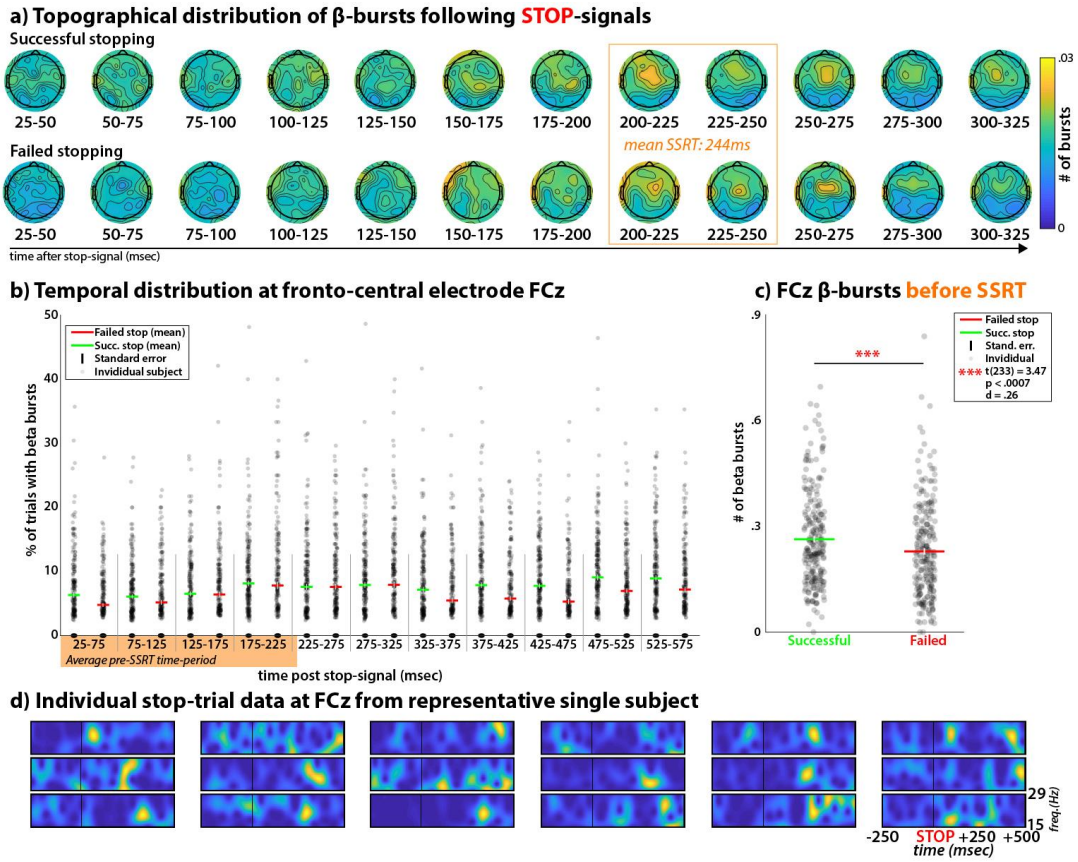
Abstract: The β-frequency band (15-29Hz) has been implicated in both movement initiation and -inhibition. In trial-averages, movement initiation is accompanied by an apparent β-band desynchronization over motor cortices, whereas movement inhibition is accompanied by increased β-band power over (pre)frontal sites. However, trial-averages may misrepresent the true nature of the β-band signal. Indeed, recent studies in both human and non-human animals suggest that β-band activity on individual trials occurs in short bursts, rather than a steady modulation. Here, we investigated the nature of scalp-recorded β-band activity on individual trials in relation to motor behavior. 234 healthy subjects underwent EEG recordings while performing the stop-signal task, in which movements have to be initiated and then sometimes inhibited. By investigating β-band activity on individual trials, we made four observations: First, during movement initiation and -inhibition, single-trial β-band activity is indeed burst-like: during initiation, the number of β-burst events over bilateral motor cortices steadily declines, an effect which lateralizes just prior to movement execution. In contrast, during inhibition (i.e., following stop-signals), the number of β-burst events over fronto-central (fc) brain regions increases (Fig. 1a,d). Second, this fc β-burst increase coincides with the end of stop-signal reaction time (SSRT, a measurement of the speed of the motor inhibition process). Third, successful stop-trials yield significantly more fc β-burst events compared to failed stop-trials prior to SSRT (Fig. 1c). Fourth, fc β-burst events on successful stop-trials are followed by a re-instantiation of bilateral β-bursting over motor cortex sites. These findings suggest that β-bursting could be a fundamental signature of the motor system, reflecting a steady inhibition of motor cortex that is suppressed during movement initiation, and can be re-instantiated by frontal areas during movement inhibition.



Disclosures: J.R. Wessel: None.

Nanosymposium

724. Human Executive Functioning

Location: Room S401

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 724.09

Topic: H.02. Human Cognition and Behavior

Support: MnDrive Brain Sciences

Title: Evidence accumulation in working memory-based decision making in human intracranial EEG

Authors: *A. B. HERMAN[1], D. P. DARROW[2], C. SAIOTE[1], M. C. PARK[2], B. Y. HAYDEN[3]; [2]Neurosurg., [1]Univ. of Minnesota, Minneapolis, MN; [3]Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Recent advances in computational psychiatry and neuroeconomics allow for model-based measurement of components of cognitive-control, a core RDoC domain. LInking these computational measures to neural circuits amenable to neuromodulation presents a major opportunity for the development of new treatments to improve decision making. Cognitive effort, a key factor in control, refers to the subjective experience of the cost of control, and influences the volitional allocation of cognitive resources during challenging tasks. Current approaches to augmenting cognitive effort are limited by a lack of understanding of the corresponding neural computations in relevant brain regions in humans. Multiple converging lines of evidence establish DLPFC as central to cognitive effort, suggesting it may be a target for neuromodulatory intervention in disorders of decision making. We examined the fine-scale neural dynamics mediating effortful decision-making in humans in DLPFC. We administered the N-back task, a classic working-memory test of cognitive effort that predicts outcomes in addiction, to epilepsy patients undergoing intracranial electroencephalography (iEEG). We analyzed the behavior using drift-diffusion equations, and found that the drift rate of evidence accumulation decreased monotonically with cognitive load in the task. Turning to the neural data, we applied targeted dimensionality reduction to the iEEG high gamma analytic amplitude traces to decode the neural evidence of progression to a decision. We find that we can decode the accumulation of evidence about working memory-based decision making within a single trial. The evidence accumulation slopes decrease monotonically with effort-level in DLPFC and correlate with the individual drift rates from the drift-diffusion model of the behavior, while the slope separation collapses in sensorimotor areas. These results reveal a novel neuro-behavioral measure of cognitive effort in memory-based decision making in DLPFC. We are now investigating this measure as a putative biomarker and target for augmenting cognitive effort with neuromodulation.

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Nanosymposium

724. Human Executive Functioning

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Presentation Number: 724.10

Topic: H.02. Human Cognition and Behavior

Title: Musical expertise modulates cognitive control mechanisms needed to resolve conflicting auditory information

Authors: *V. SHARMA[1], C. ALAIN[1], M. H. THAUT[2], F. RUSSO[3];
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Abstract: Musicians have considerable experience naming pitch-classes with verbal and semiotic tags, which can become automatic. Such experience may facilitate auditory processing even when there is conflicting information. However, there is a special instance (e.g., absolute pitch) where a strong association between perceive pitch and verbal label could also be detrimental. To better understand how neuronal systems tune to perceptual inputs and hone conscious control over abstract associational structures (e.g., language, music, etc.), we measured scalp-recorded event-related potentials while participants performed three different auditory Stroop tasks. In separate blocks of trials, participants were presented with congruent or incongruent auditory words from English language (standard auditory Stroop), Romanic solemnization or German key lexicons (the latter two versions require some knowledge of music notation). Overall, musicians with absolute pitch showed performance that was superior to musicians with relative pitch as well as non-musicians. Relative to congruent stimuli, incongruent trials generated an increased negativity that peaked between 325 and 525 ms after sound onset over the central scalp area. This modulation was larger in the auditory word Stroop than in the other two versions of the Stroop task. The neural index of conflict resolution was larger in non-musicians than musicians with absolute or relative pitch. In musicians, the reduced modulation associated with processing cognitive conflict may reflect more efficient processing.

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Nanosymposium

724. Human Executive Functioning

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Presentation Number: 724.11

Topic: H.02. Human Cognition and Behavior

Title: Contextually-driven set-switching modulates theta-band oscillatory power

Authors: *K. HWANG[1], D. CELLIER[1], M. A. PIPOLY[2];
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Abstract: Context influences how individuals select their actions. For example: one might answer a phone call in a private setting but not during a lecture, or proceed through an intersection in the absence of pedestrians but not while pedestrians are crossing. This context-dependent cognitive control demands flexibility in using contextual information to guide the selection of a stimulus-response contingency (defined as task-rule) from competing options (defined as task-sets). Switching between task-sets is known to engage a hierarchically organized prefrontal cortex (Badre and Nee, 2018), in which neural oscillations may provide a flexible mechanism for the frontal cortex to exert cognitive control (Helfrich and Knight, 2016). The goal of the present study is to investigate the oscillatory neural dynamics enabling subjects to use contextual information to flexibly switch between task-sets. We developed a set-switching task

in which healthy adult subjects were asked to make a judgment on whether a picture presented was a face or a scene based on a context cue while we collected EEG and behavioral data. While keeping the set-size (i.e., working memory load) constant, we parametrically manipulated set-switching demand by changing the probability of subjects switching between task-sets (labeled here as an extra-set-shift: ESS). We also manipulated the probability of switching task-rules within a task-set (the within-set-shift: WSS). We found that, compared to ESS and Stay trials (trials repeating the same task rule), ESS elicited longer reaction time, indicating more effortful cognitive control. Critically, compared to both stay and WSS trials, ESS trials elicited stronger theta-band power (4-8 Hz) in the right frontal EEG sensors around 220 ms after the context cue was presented. These results suggest that the frontal theta-band oscillatory signal could be a signature of neurocognitive processes for contextually-driven cognitive control.

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Nanosymposium

724. Human Executive Functioning

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Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (19K14175)

Title: Contributions of the cerebello-thalamo-cortical system to the processing of multiple rules

Authors: *T. IWABUCHI[1], T. HARADA[1], A. SHIGETOMI[2], K. J. TSUCHIYA[1], N. TAKEI[1]; [1]Res. Ctr. for Child Mental Develop., Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan; [2]Kojin Hosp., Nagoya, Japan

Abstract: Although our daily life often requires the processing of multiple rules, the underlying neural mechanisms remain unclear. The present functional magnetic resonance imaging (fMRI) study aimed to identify the neural bases of multiple rule processing. For this purpose, we adopted the “rule management” experimental paradigm (Harada et al., Sci Rep 2018). This paradigm comprised three tasks: Control, Conflict, and Multiple Tasks. In these tasks, participants were asked to choose one correct button among four buttons for each visual stimulus. The correct button was pre-determined by two rules (i.e., color and shape). For the color rule, button 1 was assigned to red, button 2 to blue, and button 3 to yellow. Similarly, as regards the shape rule, these three buttons were assigned to three specific shapes: circle, triangle, or square. Each task was separated into 20 blocks consisting of nine trials each. Each block was preceded by a cue

showing which rule had to be followed. In the Control Task, the stimuli themselves were composed of either a color or shape element alone. In contrast, the Conflict Task required participants to deal with a conflicting task, where they had to opt for the right answer for the stimulus with both color and shape elements. The Multiple Task was similar to the Conflict Task but required an extra rule, in which button 4 had to be chosen when the same button was assigned in light of the combination of the types of color and shape. Therefore, in the Multiple Task, participants had to process the color and shape rules simultaneously. Twenty-six healthy adults underwent an fMRI scan during the rule management experiment with five sessions. To identify the neural correlates of multiple rule processing, we compared the brain response to the Multiple Task with that to the Conflict and Control Tasks, and found significant activation in the bilateral thalamus, cerebellum, precuneus, posterior parietal cortex (PPC) as well as in the bilateral rostrolateral, dorsolateral, ventrolateral, and dorsomedial prefrontal cortex ($p < 0.05$, FWE corrected at cluster-level). The finding suggests that the cerebello-thalamo-cortical system contributes to multiple rule processing, consistent with a recent animal study that demonstrated the fronto-thalamic engagement in flexible rule switching (Rikhye et al., 2018 Nat Neurosci). Accuracy in the Multiple Task was significantly lower than that in the Control and Conflict Tasks, but improved over sessions, indicating progressive rule learning. Similarly, brain activity during the Multiple Task increased over sessions in the left PPC, suggesting that this area may be involved in the learning of multiple rules.

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Nanosymposium

725. Human Imaging and Connectivity

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Presentation Number: 725.01

Topic: H.02. Human Cognition and Behavior

Support: Alfred P. Sloan Research Fellow in Neuroscience (2018)

Title: Innate connectivity patterns of the visual word form area

Authors: *J. LI, D. E. OSHER, H. A. HANSEN, M. R. RHODES, A. L. HOWELL, Z. M. SAYGIN;
Psychology Dept., The Ohio State Univ., Columbus, OH

Abstract: The human brain is a patchwork of different functionally specialized areas. What determines this functional organization of cortex? One hypothesis is that innate connectivity patterns shape functional organization by first setting up a scaffold upon which functional specialization can later take place. We tested this hypothesis here by asking whether an

experience-driven region, the visual word form area (VWFA), which only becomes selective to visual words after gaining literacy, was already connected to proto language networks in neonates within one week of birth. We found that neonates showed adult-like functional connectivity, with i) language regions connecting to the putative VWFA more than with other adjacent ventral visual regions (e.g. fusiform face area, FFA) and ii) the VWFA showing the highest connectivity with language regions vs. regions adjacent to these language regions (attentional demand, speech, A1). Diffusion tractography was further used to examine structural connectivity, which provided converging evidence from two separate modalities and also offered an infrastructure/skeleton for the functional connectivity results. These data suggest that the location of the VWFA is earmarked due to its connectivity with higher-order regions like the language network, providing strong evidence that innate connectivity instructs the later development of cortex.

Disclosures: J. Li: None. **D.E. Osher:** None. **H.A. Hansen:** None. **M.R. Rhodes:** None. **A.L. Howell:** None. **Z.M. Saygin:** None.

Nanosymposium

725. Human Imaging and Connectivity

Location: Room N427

Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.02

Topic: H.02. Human Cognition and Behavior

Title: The role of prefrontal cortical morphology in the development of reasoning ability

Authors: *W. I. VOORHIES[1], J. MILLER[3], J. YAO[2], I. RAGHURAM[2], S. A. BUNGE[4], K. S. WEINER[1];
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Abstract: The human cortex folds in distinctive and predictable patterns of gyri and sulci (LaGuen et al., 2018). Deep primary sulci emerge early, while comparatively shallow tertiary sulci appear later and deepen through development. Due to their morphological variability and protracted development, a classic, but largely untested, hypothesis situates tertiary sulci as functional landmarks in slower developing cortical regions (Sanides, 1964). Here we extend this hypothesis to cognitive development, predicting that 1) tertiary sulci in lateral prefrontal cortex (latPFC) will show greater morphological variability compared to primary sulci, and 2) morphological features of tertiary, but not primary, latPFC sulci will be associated with reasoning ability in children. Cortical morphometric analyses were performed on high resolution T1-weighted MPRAGE anatomical scans in 37 participants ages 6-18, from an existing dataset (see Wendelken et al., 2017). Images were averaged during postprocessing to increase the signal-

to-noise ratio, and cortical surface reconstructions were generated using Freesurfer. 14 sulci in LatPFC were manually defined from recently proposed definitions (Petrides & Pandya, 2012). 1036 labels (14 labels per hemisphere, per subject) were assessed for 4 morphological features: mean and maximal sulcal depth, cortical thickness, and surface area. As predicted, tertiary sulci showed greater morphological variability between subjects than primary sulci. Additionally, sulcal depth was the only morphological feature that correlated with reasoning skill. Out of all sulci, only two tertiary sulci showed a positive, significant relationship with reasoning skill (β_i= 11.14($p<0.01$), β_j=10.17($p<0.05$)). Notably, a linear regression using a leave-one-out cross validation procedure with age, and depth of two latPFC tertiary sulci as predictors, explained 54.1% (MSE: 5.38) of the variance in performance on a matrix reasoning task, which was higher than models with either a) age as the sole predictor (12.9%,MSE: 9.29) or b) the depth of both tertiary and neighboring primary sulci as predictors (45.8%,MSE:5.88). Our findings demonstrate that tertiary latPFC sulci can be identified reliably in children, as well as provide strong evidence for tertiary sulci as sources of individual variability in cognition. The results corroborate prior research on the importance of latPFC development for higher cognition, and demonstrate that precise anatomical parcellations can provide valuable insights into relationships between brain anatomy and cognitive development.

Disclosures: W.I. Voorhies: None. **J. Miller:** None. **J. Yao:** None. **I. Raghuram:** None. **S.A. Bunge:** None. **K.S. Weiner:** None.

Nanosymposium

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Presentation Number: 725.03

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH107512
NIH R01NS64033

Title: Correspondence between BOLD signal and iEEG high-frequency activity during memory encoding in a pediatric sample

Authors: *L. TANG[1], E. L. JOHNSON[2], Q. YIN[1], D. MCCALL[1], S. RAMESH[1], B. THOMPSON[1], R. AGARWAL[1,3], A. LUAT[1,3], E. ASANO[1,3], N. OFEN[1,4];
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Abstract: Functional MRI (fMRI) and intracranial EEG (iEEG) are important tools for studying the neural basis of human memory. Correspondence between BOLD fMRI signals and high-

frequency iEEG activity (high-frequency power, 60-160 Hz) has been observed in both animal and human studies across cortical regions, yet such correspondence has not been assessed in children. Here, we examine such correspondence in 5 subjects (ages 5, 13, 14, 16, and 20 years) who underwent fMRI and iEEG procedures while studying visual scenes for a subsequent recognition test (fMRI: 3T Verio scanner; iEEG: 192-channel Nihon Kohden System). iEEG data were band-passed, notch filtered, and segmented into 4-s epochs. Time-frequency representations were generated using a multitapering approach (50 logarithmically spaced frequency bins, 30-250 Hz) and z-scored on a 300-ms pre-stimulus baseline via statistical bootstrapping. Subsequent memory effects were defined per electrode as the mean z-scored power for Hit > Miss trials across high-frequencies in 1-s segments from stimulus onset. fMRI data were preprocessed and general linear models were constructed to assess subsequent memory effects for Hit > Miss trials. Regions-of-interest (6-mm radius) were generated centering the coordinates of corresponding iEEG electrodes from which contrast values were extracted. Overall, subjects' memory accuracy was within the range of accuracy observed in a large sample of typically developing children who completed the same task (n = 93). Correlation analyses of all electrodes from the 5 iEEG subjects indicated good correspondence between fMRI contrast values and high-frequency subsequent memory effects in the 0-1 and 1-2 s time windows (both rs = .15, $p < .01$), but not in the 2-3 s time window ($r = .04$, $p = .42$), suggesting fMRI may capture the changes in the high-frequency iEEG activity up to 2 s post-stimulus. However, investigation of the correspondence between fMRI and iEEG subsequent memory effects in individual subjects did not yield clear between-measure correspondence. Notably, lack of correspondence on the individual level may reflect differences in memory performance between recording sessions, differences in signal-to-noise ratio between measures, or insufficient power due to low numbers of region-of-interest electrodes in individual patients. Taken together, we provide initial evidence suggesting that while there is good correspondence between fMRI and iEEG high-frequency subsequent memory effects across a small sample of pediatric subjects, only limited correspondence may exist on an individual level.

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Nanosymposium

725. Human Imaging and Connectivity

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Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.04

Topic: A.09. Adolescent Development

Support: NIH R01 MH 117601
NIH R01 MH 116147

Title: Family history of suicide may have a sex-specific effect on brain structure in adolescents

Authors: *A. H. ZHU, P. M. THOMPSON, N. JAHANSHAD;
USC, Marina del Rey, CA

Abstract: Suicidal behaviors are complex traits with both genetic and environmental risk factors. In a study combining suicide attempters with psychiatric patients and relatives, both with no history of suicidal attempts, Jollant et al. (2018) found smaller volumes in frontal and temporal brain regions in adults with a family history of suicide (FHoS). However, the effects of FHoS have yet to be assessed on childhood brain development. Here we aimed to investigate the impact of FHoS on adolescent brain development using data from the Adolescent Brain Cognitive Development (ABCD) Study, and to determine if the effect differs in males compared to females. At baseline, children in the ABCD Study are aged 8-11 years old. As part of the study, the caretakers of over 10,000 children filled out the ABCD Family History Assessment. Of these, 2,011 children (949 females) had a first or second degree family member who died by suicide. 8,100 children (3872 females) did not have any FHoS and were selected as controls. FreeSurfer morphometric data is provided by the ABCD Study. Cortical volume data was extracted, and each region of interest (ROI) was bilaterally averaged. Intracranial volume (ICV) was also extracted and demeaned by sex to remove sex effects. Based on prior studies, ROIs were limited to the frontal and temporal lobes. Covariates included age (months), sex, age-by-sex, ICV, and combined family income. Males and females were then evaluated separately. Multiple comparisons were accounted for using the false discovery rate correction. Case-control groups did not differ significantly in age or ICV ($p > 0.1$). Combined family income was significantly higher in the full set and male subset control groups ($p < 0.001$) but did not differ in the female subset ($p = 0.16$). The volumes of the caudal middle frontal ($q < 0.006$), lateral orbitofrontal ($q < 0.001$), pars opercularis ($q = 0.019$), precentral ($q = 0.019$) and transverse temporal ($q = 0.01$) regions were significantly larger in all children with FHoS compared to controls ($q = 0.045$). In the male subset, the lateral orbitofrontal ($q = 0.039$) was significantly larger in the FHoS group, while the caudal middle frontal ($q = 0.01$) was significantly larger in the female FHoS group. When limited to children of first degree FHoS relatives, the lateral orbitofrontal ($q = 0.047$) is the only region that remains significantly larger in the full set. Gray matter loss is expected in children this age, and delayed synaptic pruning may explain the larger frontotemporal volumes rather than the smaller volumes found in adults. By identifying brain differences in children at possible risk for suicidal behaviors, we may be able to identify novel, targeted treatments and care.

Disclosures: A.H. Zhu: None. **P.M. Thompson:** 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.; Biogen, Inc. **N. Jahanshad:** 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.; Biogen, Inc..

Nanosymposium

725. Human Imaging and Connectivity

Location: Room N427

Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.05

Topic: I.07. Data Analysis and Statistics

Title: Do individuals with autism have face recognition impairments? An empirical meta-analysis across 85 studies

Authors: *J. W. GRIFFIN, R. BAUER, S. SCHERF;
The Pennsylvania State Univ., University Park, PA

Abstract: Difficulties in face recognition are commonly reported in individuals with autism spectrum disorders (ASD). However, empirical findings across studies are mixed regarding the presence and consistency of this difficulty. For example, one summary review of the literature reported that only 50% of studies found ASD groups performing worse than typically-developing (TD) groups (Weigelt et al., 2014). A more recent review reported only 9 of 25 studies showed face recognition impairments in ASD groups (Tang et al., 2015). In spite of these findings, both reviews concluded that people with ASD have deficits in face recognition abilities. The goal of the current work was to conduct a *quantitative meta-analysis* of studies comparing face recognition abilities in ASD and TD groups to determine whether there is a consistent relative impairment in these abilities among ASD individuals and if so, to quantify the magnitude of the relative impairment in terms of an effect size. We also estimated the relative contributions of age, full scale IQ, sex, task paradigm, and data quality on this effect. We focused exclusively on studies of face recognition, which included paradigms that required encoding, delay and recall of face identity representations. The literature search within PubMed yielded 85 unique articles that contained 118 effect size estimates. The final sample included 2668 ASD and 2830 TD participants who ranged in age from 5-44 years. We conducted a multilevel, random-effects meta-analysis to estimate a summary effect size using Hedge's G. Results revealed that ASD individuals do have a relative impairment in face recognition abilities: Hedge's G = -0.80, 95% CI [-0.94, -0.65]. There was also significant heterogeneity (I2 = 78.34%) across studies that was not captured by the variables of interest. This is the first meta-analyses to empirically determine that autistic individuals, as a group, do appear to have consistent difficulties in face recognition compared to TD individuals and the effect is of moderate size and consistent across age, IQ, sex, and data quality. The residual discrepancies across studies may be due to variations in autism symptoms and/or individual differences in skill level with face recognition abilities in the ASD and/or TD groups. This impairment may contribute to the social communication difficulties that autistic individuals experience.

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Nanosymposium

725. Human Imaging and Connectivity

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Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.06

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

Support: National Institutes of Health (R01 EY019924-08)
Research to Prevent Blindness/Lions Club International Foundation
Deborah Munroe Noonan Memorial Research Fund O'Brien Award

Title: Structural-functional network coupling in cerebral compared to ocular visual impairment

Authors: C. M. BAUER[1], E. S. BAILIN[2], J. SEPULCRE[3], *L. B. MERABET[4];
[1]Harvard Med. School, Massachusetts Eye and Ear, Boston, MA; [2]Mass. Eye and Ear -- Harvard Med. Sch., Boston, MA; [3]Radiology, Harvard Med. Sch. - Gordon Ctr. for Med. Imaging, Boston, MA; [4]Ophthalmology, MEEI- SERI Harvard Med. Sch., Boston, MA

Abstract: Background: Dramatic structural and functional brain reorganization have been reported in ocular blindness. However, neuroplastic changes in the setting of cerebral/cortical visual impairment (CVI) remain unknown. In this study, we employed a combined neuroimaging approach using high angular resolution diffusion imaging (HARDI) and resting state functional connectivity (rsfc) MRI to explore structural (white matter) and functional (resting state) connectivity of large-scale brain networks in individuals with CVI compared to ocular visual impaired (OVI) and neurotypical sighted controls. **Methods**: Data were collected using a 3T Philips Achieva scanner. Structural imaging sequences included a high resolution T_1-weighted structural image for anatomical reference and HARDI was acquired using a single shot EPI sequence (TE 73 ms, TR 17844 ms, B = 3000, 64 directions). rsfcMRI was acquired using a 7 min single shot EPI sequence (TE 30 ms, TR 3000 ms) sensitive to blood-oxygen-level-dependent (BOLD) contrast. A cohort of individuals with CVI (n=5), OVI (n=12), and controls (n=26) were instructed to stay awake during scanning with their eyes closed and allow their minds to "wander". Using a graph theoretical analysis, topological properties (with global efficiency as the primary network outcome) and the degree of coupling between structural and functional networks were examined. **Results**: When compared to both OVI and controls, global efficiency for structural connectivity was markedly reduced in CVI, suggestive of inefficient network architecture for information exchange. However, global efficiency for functional connectivity was comparable across groups. Finally, while structural-functional coupling was reduced in CVI compared to controls, evidence of increased network coupling was observed in OVI. **Conclusions**: These results suggest that in the case of CVI, functional connectivity networks embed differently from structural networks and further, there is evidence of functional reorganization even in the context of large scale disruption of white matter structural connectivity. These preliminary findings demonstrate the importance of multi-modal network

based analyses to help better understand the underlying neurophysiology and differences between cerebral compared to ocular based visual impairment.

Disclosures: C.M. Bauer: None. **E.S. Bailin:** None. **J. Sepulcre:** None. **L.B. Merabet:** None.

Nanosymposium

725. Human Imaging and Connectivity

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Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.07

Topic: B.09. Network interactions

Support: DoD Grant W81XWH-15-2-0032

Title: Reorganization of intrinsic neural networks associated with tinnitus

Authors: *S. SHAHSAVARANI[1], R. KHAN[2], S. SCHMIDT[2], Y. TAI[1], F. HUSAIN[1]; [1]Speech and Hearing Sci., [2]The Neurosci. Program, Univ. of Illinois At Urbana-Champaign, Champaign, IL

Abstract: Resting-state functional magnetic resonance imaging (fMRI) has been widely used to investigate the organization of intrinsic neural networks and its correlation with neurological disorders. Here, we investigated the association between a hearing disorder, namely tinnitus, and reorganization of intrinsic neural networks. Tinnitus is a condition in which patients perceive sounds in the absence of an external source. The tinnitus patient population is highly heterogeneous in terms of etiology, age, hearing sensitivity, and severity of symptoms. Previous studies from our lab showed that tinnitus was associated with reduced coherency in the default mode network (DMN) and changes in the dorsal attention network (DAN). In this study, resting-state fMRI data were obtained for 10 minutes from a relatively large group of participants including 47 patients with tinnitus (19 females; 79% with hearing loss; mean age = 52.59 years) and 30 controls without tinnitus (15 females; 40% with hearing loss; mean age = 47.73 years). Using Tinnitus Functional Index (TFI) scores, tinnitus patients were divided into those with mild tinnitus (TFI < 25; n=31) and those with bothersome tinnitus (TFI >= 25; n=16). Preprocessing was performed using Statistical Parametric Mapping software (SPM12). Seed-based analysis was conducted to compute resting-state functional connectivity using the Functional Connectivity Toolbox (Conn) while accounting for age, hearing status, and tinnitus severity. Four resting-state networks were investigated: (1) DMN, (2) DAN, (3) the auditory network, and (4) the salience network. The results showed that there were no significant differences between patients and normal hearing controls for all the networks. Compared with hearing loss controls, bothersome tinnitus was correlated with increased coupling between the DMN and supramarginal gyrus (a part of the task-positive network), and mild tinnitus was associated with reduced functional connectivity between DAN and right superior frontal gyrus (a region that plays a role in attention

orientation), indicating tinnitus-related changes in both DMN and DAN. Moreover, patients with mild tinnitus showed greater functional connectivity between the salience network and lateral occipital cortex than hearing loss controls. Patients with bothersome tinnitus also showed greater functional connectivity between the salience network and precuneus (a major hub in DMN), relative to those with mild tinnitus. Our findings highlight the importance of non-auditory intrinsic networks including DMN, DAN, and the salience network in differentiating tinnitus from non-tinnitus groups and for indexing severity.

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Nanosymposium

725. Human Imaging and Connectivity

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Presentation Number: 725.08

Topic: B.09. Network interactions

Support: Canadian Institutes of Health Research (CIHR) Doctoral Award (357215) received by J. Baarbé
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Dystonia Medical Research Foundation Canada Fellowship Grant received by K.J. Lizarraga

Title: Transcranial magnetic stimulation of the right posterior parietal cortex inhibits left motor short interval intracortical facilitation and parietal-motor connectivity

Authors: *J. K. BAARBÉ[1], M. VESIA[2], C. GUNRAJ[1], G. JEGATHEESWARAN[1], M. J. BROWN[3], K. J. LIZARRAGA[1], A. WEISSBACH[1], N. M. DRUMMOND[1], J. SARAVANAMUTTU[1], C. RINCHON[1], R. CHEN[1];
[1]Toronto Western Hosp., Toronto, ON, Canada; [2]Univ. of Michigan, Sch. of Kinesiology, Ann Arbor, MI; [3]Kinesiology and Hlth. Sci., California State Univ. Sacramento (CSUS), Sacramento, CA

Abstract: The posterior parietal cortices play an essential role in sensorimotor processing during hand reach and grasp movements. However, it is still unclear how they influence corticospinal excitability. Previous studies have shown that transcranial magnetic stimulation (TMS) of the

right posterior parietal cortex (RPPC) enhances left motor cortex excitability, yet it inhibits left parietal-motor cortex connectivity (LPPC-LM1). Although homologous right and left parietal areas are structurally connected and likely influence motor outputs, the right parietal cortex interacts directly with left motor and pre-motor areas, and such functional connectivity can be mediated by several anatomical pathways. We hypothesized that the RPPC engages facilitatory and inhibitory motor circuits in the left hemisphere and thereby influences LPPC-LM1 connections. Fourteen healthy adults (7 females, aged 23-64 years) were tested with neuronavigated TMS. Experiment 1 tested the effects of LPPC stimulation on LM1 excitability and the effects of RPPC stimulation on LPPC-LM1 connection. Experiment 2 and Experiment 3 tested the effects of RPPC stimulation on left intracortical motor circuits, short interval intracortical facilitation (SICF) and short interval intracortical inhibition (SICI), respectively. Although LPPC stimulation did not significantly change LM1 excitability, RPPC stimulation inhibited LPPC-LM1 connection, likely through its effects on left M1. Indeed, LM1 SICF was inhibited by RPPC stimulation but was unaffected by LPPC stimulation. The reduction of LM1 SICF by preceding RPPC stimulation correlated with the inhibitory effect of RPPC stimulation on LPPC-LM1 connection. LM1 SICI was unaffected by LPPC (LPPC-SICI) stimulation, but when RPPC stimulation preceded LPPC-SICI, greater cortical inhibition was observed. Our findings suggest that the right posterior parietal cortex directly influences left M1 excitability via sensorimotor networks in which intracortical LM1 circuits play an important role.

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Nanosymposium

725. Human Imaging and Connectivity

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Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.09

Topic: B.09. Network interactions

Title: Alpha, beta, and gamma-band electrocorticographic responses to auditory tones presented in broadband-noise are consistent with the effects of temporal-integration and cortical gain-control

Authors: *M. RAGHAVAN;
Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Local engagement of the cerebral cortex by sensory stimuli or cognitive tasks is typically manifested in the electrocorticogram (ECoG) as an increase in power within the gamma bands (>40 Hz) accompanied by a decrease in power within the alpha (8-13 Hz) and beta (13 to 30 Hz) frequency-bands. Many recent studies also suggest that high-gamma (>70 Hz) power is

correlated with neuronal population firing-rates. While the task and stimulus-dependence of these responses have been studied extensively using many different paradigms, it is not known how their latencies and magnitudes are shaped by stimulus intensity or the presence of adapting stimuli. ECoG responses to auditory stimuli were recorded from 64-contact (8X8) subdural grid electrodes in four patients undergoing invasive EEG studies as part of evaluations prior to epilepsy surgery. The patients performed an auditory odd-ball tone-recognition task where probe-tones of a fixed amplitude and 400 ms duration were presented on a background of auditory broadband-noise. The noise background started 400 ms before tone-onset and continued for 400 ms after cessation of the tone. The intensity of the noise was randomly switched across trials in order to achieve three different signal-to-noise-ratios for the probe-tone. The electrodes with the maximal response were in the vicinity of Heschl's gyrus in all patients. At these electrode-locations, increases in gamma-band power were sustained for ~ 300 ms, while alpha and beta-band power showed an transient initial increase in power before sustained decreases after onsets of both the noise and subsequent tone stimuli. At the onset of the background-noise, high-gamma response latency is a *decreasing* function of noise-intensity, while the magnitude of the response *increases*. At the onset of the tone that appears on the noise background, high-gamma response latency is an *increasing* function of noise-intensity, while both the magnitude of the high-gamma response and that of the event-related potential (ERP) *decreases*. These findings suggest a model of ECoG reactivity wherein neuronal firing is down-regulated by an input-gain reduction which is maximally effective after stimuli have been temporally integrated for >100 ms. Sustained attenuation of alpha and beta power after an initial transient increase would be consistent with the effects of such a gain-reduction if these oscillations are sustained via feedback loops that include the variable-gain, presumably in the cortex.

Disclosures: M. Raghavan: None.

Nanosymposium

725. Human Imaging and Connectivity

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Time: Wednesday, October 23, 2019, 1:00 PM - 3:30 PM

Presentation Number: 725.10

Topic: B.09. Network interactions

Support: NIMH BRAIN Initiative Grant MH111439

Title: Fluctuating inter-regional delays in the auditory hierarchy of the human cortex

Authors: *J.-Y. MOON[1], K. MÜSCH[2], C. E. SCHROEDER[3], C. J. HONEY[2];
[1]Dept. of Psychological and Brain Sci., [2]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [3]Nathan Kline Inst. - Translational Neurosci. Div., Columbia Univ. Col. of Physicians and Surgeons, Orangeburg, NY

Abstract: Motivation: Bottom-up information flow occurs when sensory information is sent to higher order regions of the cerebral cortex, and top-down information flow occurs in the reverse direction. How does the balance of the bottom-up verses top-down signaling vary over time? We addressed this question by measuring intracranial potentials in the human brain during a naturalistic auditory processing task, and characterizing the time delay (latency) between consecutive processing stages. We asked: (i) are inter-regional delays fixed or variable over time? (ii) how do the latencies between processing stages depend on the electrophysiological state of local circuits and stimulus characteristics?
Methods: We recorded electrocorticographic (ECoG) signals from the auditory processing pathways of 6 human participants. Each participant listened to two repetitions of a 7-minute narrative. In sliding time-windows, we computed the cross-correlations of the voltage signal between electrode pairs. For each electrode and electrode-pair in each time window, we identified: the time lag of maximal inter-electrode correlation, the 8-12 Hz alpha power, and the mean broadband high-frequency power.
Results: Consistent with prior reports [Jacobs, Zaghloul] we found that, the auditory pathway exhibited a gradient of delays, with posterior temporal region leading anterior temporal regions on average. However, inter-electrode delays fluctuated over time (mean of s.d. = 5.7ms across time windows). These delay fluctuations were reliable across repetitions of the same natural auditory stimulus (e.g. Spearman rho = 0.25 across repetitions). Moreover, we observed longer inter-channel latencies during bursts of alpha power (*propagating state*), and shorter latencies during bursts of broadband power (*synchronized state*). Finally, the alpha bursts and propagating states occurred preferentially in the silent boundaries between sentences.
Conclusions: We found that cortico-cortical coupling delays are dynamic in the human brain. Inter-regional delays in the auditory pathway varied over time in a reproducible manner across repeats of the same minutes-long stimulus. Also, the long-latency "propagating states" in the auditory pathway robustly co-occurred with bursts of alpha-band power, which are implicated in modulating corticocortical and thalamocortical interactions (van Kerkoerle et al., 2014).

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Nanosymposium

726. Personalized Brain Signatures

Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.01

Topic: H.02. Human Cognition and Behavior

Support: Defense Health Agency Research and Development Directorate (J9) grant H1739

Title: Changes in visual processing during low-oxygen exposure: Evidence from visual mismatch negativity and P3a

Authors: *K. J. BLACKER[1,2], T. R. SEECH[3], M. J. KINNEY[1], M. E. FUNKE[1];
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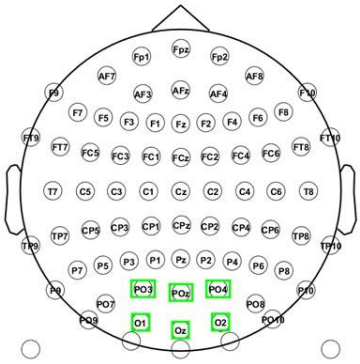
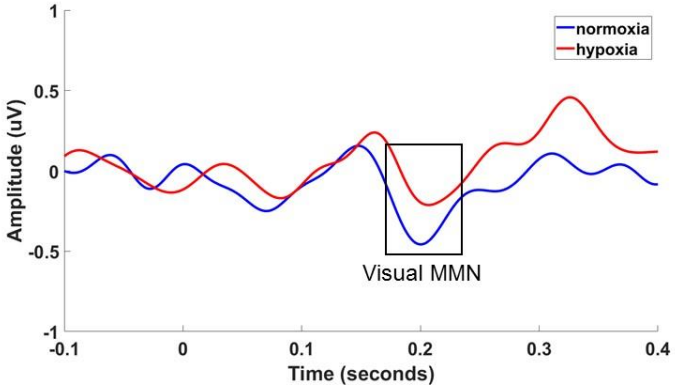
Abstract: Previous work has demonstrated that exposure to reduced levels of breathable oxygen negatively impacts a variety of perceptual and cognitive systems. In particular, there is a body of work that suggests that the visual system is one of the earliest affected by low-oxygen exposure. While the majority of previous studies have relied on self-report and behavioral response testing, the use of event-related potentials (ERPs) as a novel tool to monitor the effect of hypoxia exposure in humans has recently been investigated by our group. Specifically, mismatch negativity (MMN) and P3a components are evoked in response to unattended changes in background sensory stimulation. The MMN/P3a complex is passively elicited, requires no overt behavioral response or even awareness on the part of the participant, and reflects the brain's ability to efficiently detect changes. In the current study, participants (n=20) completed a continuous visuomotor tracking task while EEG was recorded. In addition to the tracking task, a series of photometrically isoluminant reversing color checkerboard patterns were presented in the periphery while occasionally an "oddball" color checkerboard was presented. The MMN/P3a was assessed in response to the oddball stimuli compared to the standard stimuli. Participants completed two sessions in counterbalanced order: one at a simulated altitude of 17,500 ft (i.e., hypoxia) and one at approximately sea-level (i.e., normoxia). Results demonstrated that the MMN/P3a signal complex was sensitive to hypoxia exposure, showing a significantly reduced amplitude during hypoxia exposure compared to the normoxia condition. Our results suggest that during low-oxygen exposure the ability to detect environmental changes and process sensory information efficiently is impaired. The MMN/P3a may represent an early and reliable predictor of sensory and cognitive deficits during hypoxia exposure, which may be of great use to the aviation and/or diving communities.





Disclosures: K.J. Blacker: None. **T.R. Seech:** None. **M.J. Kinney:** None. **M.E. Funke:** None.

Nanosymposium

726. Personalized Brain Signatures

Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.02

Topic: H.02. Human Cognition and Behavior

Support: ARC Centre for Excellence in Cognition and Its Disorders
Bial Foundation 70/16

Title: Reduced medial-lateral prefrontal cortex functional connectivity in high hypnotic suggestibility

Authors: *D. B. TERHUNE;
Goldsmiths, Univ. of London, London, United Kingdom

Abstract: Hypnotic suggestibility is the principal factor underlying response to hypnosis and confers a set of benefits and vulnerabilities with implications for healthy and pathological cognition. Previous research has highlighted atypical patterns of functional activation or connectivity in medial prefrontal and frontal-parietal networks but most studies have included problematic control groups and focused on the impact of a hypnotic induction rather than the neurophysiological characteristics of highly suggestible (HS) individuals. In a double-blind design, we used magnetoencephalography (MEG) to measure resting state network (RSN) activation and functional connectivity (weighted phase lag index) patterns in medium suggestible (MS) (control) and HS participants in order to test the predictions that HS participants would display reduced connectivity within and between medial prefrontal and lateral prefrontal networks in alpha2 (11-13Hz) and beta1 (13-20Hz) bands. Phase amplitude coupling (PAC) was used to identify canonical RSNs of interest (medial prefrontal network [mPFN] and right frontal-parietal network [rFPN]) and control networks (left- and right- default mode networks [lDMN and rDMN], visual network, and dorsal attention network [DAN]). HS participants displayed lower alpha2 power across sensors than MS participants but the two groups did not exhibit differential power in any of the RSNs. HS participants displayed selectively lower intra-network functional connectivity in mPFN and rFPN in the alpha2 and beta1 bands and lower mPFN-rFPN inter-network functional connectivity in both bands than MS participants. These results suggest that high hypnotic suggestibility is characterized by reduced communication within and between frontal networks that support higher-order psychological functions.

Disclosures: D.B. Terhune: None.

Nanosymposium

726. Personalized Brain Signatures

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Presentation Number: 726.03

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant RO1DC013825
National Science Foundation Graduate Research Fellowship Program under Grant No. DGE-1247312
Ford Foundation Pre-doctoral Fellowship
Neuroscience Scholars Program (SfN)

Title: Neural measures of auditory selective attention suggest diminished top-down control in ADHD

Authors: *J. KWASA[1], B. SHINN-CUNNINGHAM[2];
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Abstract: People with Attention Deficit Hyperactivity Disorder (ADHD) tend to have system-wide cognitive deficits that lead to distractibility and inefficiencies in organizing, vigilance, and inhibition. Selective attention is the ability to preferentially pay attention to a single stimulus within a complex sensory environment, which requires cognitive control. Individuals greatly differ in auditory selective attention performance, even in the absence of hearing loss and regardless of ADHD diagnosis. Using 64-channel human electroencephalography (EEG), we assessed behavioral performance and brain measures of selective attention in a cohort of young adults with normal hearing across the ADHD spectrum, including neurotypical controls, to assess if ADHD status has an influence on this particular type of sensory processing.
Participants listened to three time-staggered, spatially lateralized streams of speech consisting of permutations of the syllables bah, dah, and gah. Participants were prompted to report the order of the syllables presented from a central "target" stream or a left lateralized "surprise" stream and to always ignore a right lateralized "distractor" stream. The surprise stream either began at a random delay or did not play at all. This paradigm produces two attentional states: focal attention, where only the central target stream was attended, and broad attention, where listeners had to monitor the target stream but be prepared for a spatial attention switch to report the surprise stream. Concurrent EEG was recorded and analyzed for evoked neural responses.
Results: There were no significant group differences in behavioral performance between ADHD and neurotypical participants for either attention condition (focal / broad). However, the amplitudes of ADHD participants' neural responses modulate significantly less than those of neurotypical controls in response to differing attentional demands. Further, this effect was only significant when surprise stimuli overlapped in time with target stimuli, the most challenging task condition, due to energetic masking. These results support the idea that adults with ADHD might have unseen deficits in cognitive control that are undetectable by performance on a task (like most ADHD diagnostic tests). Additionally, individual differences in performance did correlate to neural response amplitudes, indicating that evoked EEG activity could serve as a useful neural correlate of selective attention ability in the general population. Developing

objective measures of cognitive control like this is pivotal for research on attentive listening in complex auditory environments such as noisy classrooms.

Disclosures: J. Kwasa: None. **B. Shinn-Cunningham:** None.

Nanosymposium

726. Personalized Brain Signatures

Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.04

Topic: H.02. Human Cognition and Behavior

Support: NIH MH 108591
NSF BCS 1558497

Title: Transforming the task-free connectome to predict task-specific connectomes

Authors: *K. YOO[1], M. D. ROSENBERG[1,4], Y. KWON[1], D. SCHEINOST[2], R. T. CONSTABLE[3], M. M. CHUN[1];
[1]Dept. of Psychology, [3]Dept Diagnos. Radiol, [2]Yale Univ., New Haven, CT; [4]Psychology, Univ. of Chicago, Chicago, IL

Abstract: The task-free (rest) functional connectome predicts individual differences in behavior (*Finn et al., 2015; Rosenberg et al., 2016*), while the task-evoked connectome can predict behavior with higher accuracy (*Greene et al., 2018*). Compared to task-free scans, however, task scans can be more difficult to collect consistently across studies and sites. Here we introduce a transformation method to generate individual task-evoked connectomes from task-free scans, improving behavioral predictions.
Using Human Connectome Project fMRI (S1200; n=316 after excluding relatives and individuals who did not complete all scans with low head motion), we constructed 8 functional connectomes for each participant from rest and task scans. In a 10-fold cross-validation scheme, we trained a model to predict each individual's 7 task connectomes (emotion, gambling, language, social, relational, motor, and working memory) from their task-free connectome using principal component analysis and partial least square regression.
Predicted task connectomes (*P*) resembled empirical task connectomes (*T*), as similarity between *P* and *T* was significantly higher than similarity between the empirical rest (*R*) and *T* for all tasks ($p < 0.01$, Figure 1A). Demonstrating specificity, within-task similarity between *P* and *T* (on-diagonal in Figure 1B) was higher than cross-task similarity (off-diagonal). Brain fingerprinting (Finn et al., 2015) demonstrated that the *P* successfully identified *T* of the same task (Figure 1C). Finally, *P* better predicted fluid intelligence than *R* (Figure 1D).
In summary, based solely on the task-free data, our state transition model predicts task-evoked connectomes with a high degree of specificity across 7 task states. In doing so, the model

amplifies behaviorally relevant individual differences in task-free connectivity patterns, thereby improving fluid intelligence predictions. Predicting task from task-free connectome could have practical implications, such as estimating the task connectome of participants lacking task scans or from patients unable to perform tasks.

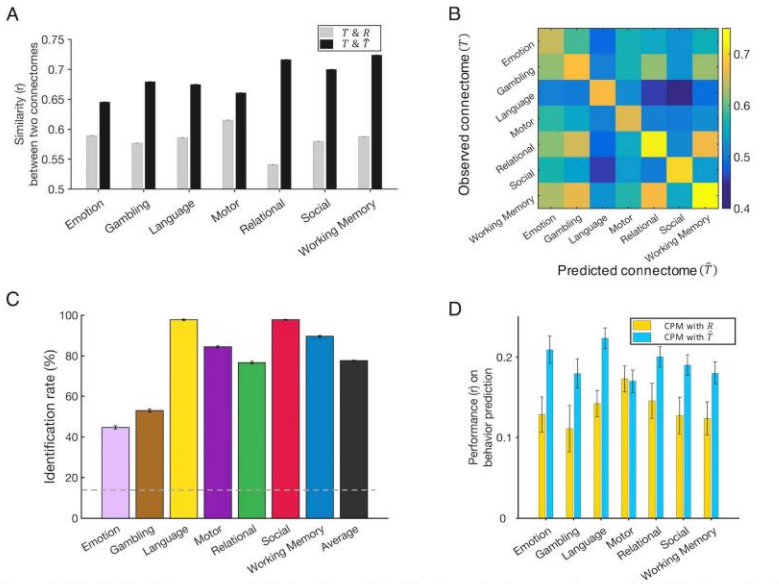

Figure 1. Similarity between predicted and empirical task-evoked connectomes. Panel A shows that predicted task connectomes resemble empirical task-evoked connectomes more than the rest connectome does. R: rest (task-free) connectome. T: empirical task connectome. $\hat{T}$: predicted task connectome. This indicates that the state transition model accurately predicts individuals' task-evoked connectomes. **Panel B** represents spatial similarity between the predicted and the empirical task-evoked connectomes with 7 different tasks. On-diagonal elements exhibit the highest similarity within each column. For example, predicted working memory connectome is most similar to the observed connectome of the working memory task than the other tasks. This similarity matrix was obtained for each individual and then averaged. **Panel C** shows successful identification of empirical task connectomes by predicted task connectomes. Given the 7 tasks, the chance level is 14.3% (=100/7), represented by a horizontal gray dashed line. In all 7 tasks, the predicted connectomes exhibit significantly higher success identification rate. **Panel D** indicates that the predicted task-evoked connectome better predicts individual differences in fluid intelligence than the observed rest connectome does, except the case of motor task.

Disclosures: K. Yoo: None. **M.D. Rosenberg:** None. **Y. Kwon:** None. **D. Scheinost:** None. **R.T. Constable:** None. **M.M. Chun:** None.

Nanosymposium

726. Personalized Brain Signatures

Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.05

Topic: H.02. Human Cognition and Behavior

Title: Nodes of DMN involved in general intelligence

Authors: *A. YADAV[1], P. LALWANI[2], H. SURI[2], R. JEJURIKAR[1], A. PURUSHOTHAM[3]; [1]NCBS, Bangalore, India; [2]IISER Pune, Pune, India; [3]Baylor Col. of Med., Houston, TX

Abstract: General intelligence (or g factor) is a consolidated measure of diverse cognitive domains. Role of Default Mode Network is well established in implicit abilities. However, studies regarding the contribution of DMN in general intelligence has been very limited. In order to identify the robust correlate, we harnessed the positive manifold nature of g. Using a test battery with tests in the Logic, Language, Executive and Fluency domains, we calculated multiple G factors from subsets of the tests (one from each domain). Three structural brain features: Grey matter density, Cortical thickness and Local gyrification index (LGI), were used for both ROI and whole brain analysis in healthy young adults.
Recruitment/Behaviour - Healthy individuals with fluent English, between the ages of 22 and 35 years were recruited (N=98, M/F = 52/46). A test battery of 4 cognitive domains with 9 tests was administered to these individuals in two sessions. MRI - High resolution T1 MRI scans were acquired using a 20-channel RF head coil at a SIEMENS SKYRA 3 Tesla MR scanner located in HCG Hospital, Bangalore (N = 44, M/F = 28/16). (TE 3.9 ms, TR 8.3 ms, No. of slices 192, FOV 240*240, Slice thickness 1 mm). G factor analysis - Factor analysis (without rotation) of a subset of test scores was used to obtain the G factor. One test from each cognitive domain was used giving us a total of 24 G scores. MRI Image processing - After pre-processing (including skull stripping, motion correction, normalization, co-registration), for grey matter intensity, voxel-based morphometry was performed using FSL, and cortical thickness and LGI were calculated using Freesurfer. For voxel-based analysis, after-randomization cluster level threshold was set at $p<0.05$. For surface analysis, vertex level threshold = $p<0.01$ and cluster level threshold = $p<0.05$ after randomization. GLM was preformed regressing out handedness and sex. ROI based analysis was preformed using Destrieux Atlas.
Results: Brain regions that were common to at least half of the 24 G-scores were taken as a significant correlate of g. In ROI based analysis, a positive correlation was found in Posterior Cingulate gyrus (dorsal/ventral), temporal middle gyrus all in the right hemisphere, apart from occipital-temporal sulci which were present in both for LGI. For thickness, Posterior Cingulate gyrus ventral, Occipital temporal medial parahippocampal gyrus, and temporal inferior gyrus in right hemisphere showed a negative correlation. We found similar brain regions in whole brain analysis which further reinforce our claim.

Disclosures: **A. Yadav:** None. **P. Lalwani:** None. **H. Suri:** None. **R. Jejurikar:** None. **A. Purushotham:** None.

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Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.06

Topic: H.02. Human Cognition and Behavior

Support: fMRI Pilot

Title: Reliable, person-specific functional architecture derived from human connectome project task data

Authors: ***M. SIMMONITE**, D. KHAMMASH, A. M. BELTZ, T. A. POLK;
Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Different parts of the brain perform different functions, and identifying those parts and determining their function is a central goal of neuroscience. Anatomical subdivisions based on gross anatomy or cytoarchitecture are useful, but are based on structure rather than function. Functional MRI is sometimes used to try to map the brain's functional architecture, but we would argue that this potential has not yet been fully realized. One important reason is that most neuroimaging studies average across participants. This approach works well if participants recruit the same neural circuits and if their brains are organized the same way. However, different people often employ different strategies to perform the same task, and human brains are notoriously heterogeneous. We propose to overcome this problem by analyzing functional architecture at the individual participant level. We hypothesize that different people have quite different functional architectures, but that the architecture within an individual is relatively stable. We tested this idea by analyzing task-based neuroimaging data that was acquired from the same participants at two different time points as part of the Human Connectome Project (n= 45, 44% female). Specifically, we used k-means clustering to derive person-specific maps of functional architecture and compared the test-retest reliability of these maps within the same person against the similarity of maps derived from different people. As predicted, within-person reliability was significantly higher than between-person similarity across multiple parcellation granularities. These results demonstrate that the unique features of person-specific functional parcellations are not noise, but rather reflect reliable characteristics of each individual’s functional architecture.

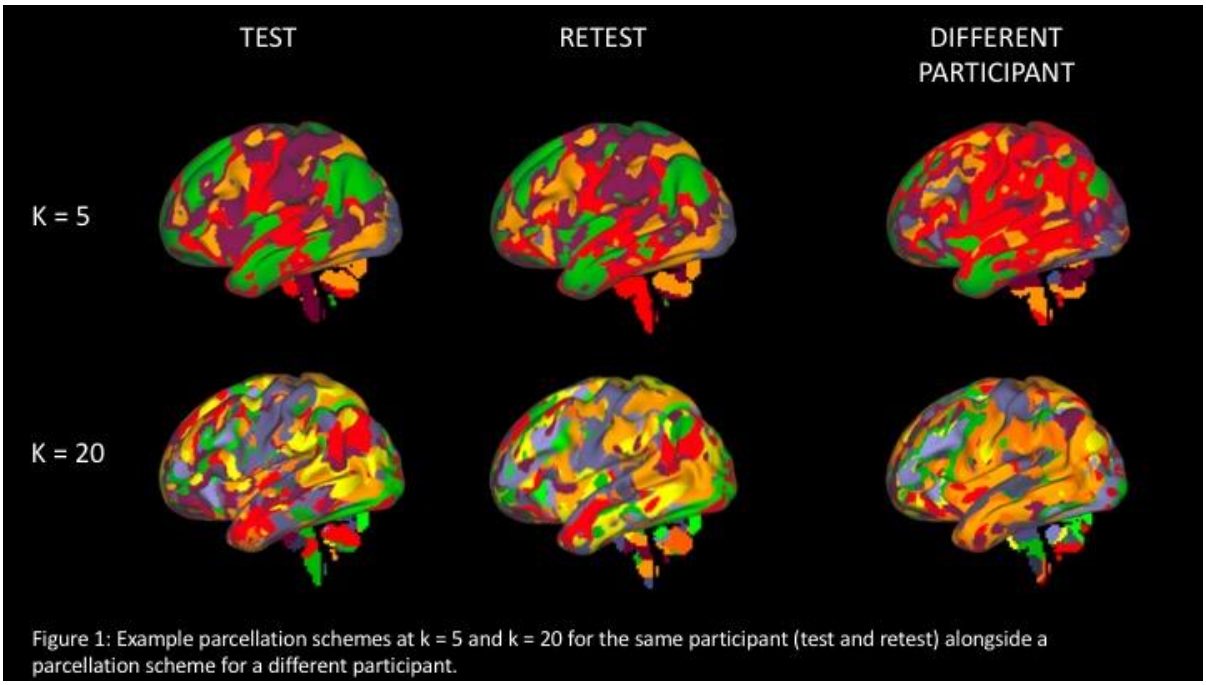

Figure 1: Example parcellation schemes at k = 5 and k = 20 for the same participant (test and retest) alongside a parcellation scheme for a different participant.

Disclosures: **M. Simmonite:** None. **D. Khammash:** None. **A.M. Beltz:** None. **T.A. Polk:** None.

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Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.07

Topic: H.02. Human Cognition and Behavior

Support: Leverhulme Early Career Fellowship ECF-2017-151
Wellcome Trust Seed Grant 109719/Z/15/Z

Title: Reduced reliance on pitch cues for speech perception in amusia: A neural basis

Authors: ***K. JASMIN**[1], F. DICK[2], L. STEWART[3], L. L. HOLT[4], A. TIERNEY[1];
[1]Birkbeck Univ. of London, London, United Kingdom; [2]Birkbeck/UCL Ctr. For NeuroImaging, London, United Kingdom; [3]Goldsmiths Univ. of London, London, United Kingdom; [4]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Congenital amusia is characterized by disordered processing and memory related to pitch. Behavioral experiments have shown that individuals with amusia rely less (than controls) on pitch when understanding speech. However, the extent to which this 'pitch neglect' manifests cortically is unknown. Here we used functional magnetic resonance imaging to scan 15

individuals with amusia and 15 controls while they performed a phrase boundary detection task. On each trial, auditory and visual sentences needed to be matched by relying on pitch cues, duration cues, or both combined. Because previous reports have indicated disordered connectivity in amusia, we used a data-driven analysis approach to evaluate correlated neural activity across all possible combinations of brain areas, and identify the strongest differences in connectivity between groups and conditions. Group differences in functional connectivity (Control > Amusia) were strongest in four patches of inferior frontal cortex. Connectivity with these 'seed' patches was examined with respect to the rest of the brain. The most prominent decreases were between left inferior frontal cortex (classically involved with language processing) and right auditory and insular cortices (areas associated with pitch processing). No differences between the experimental conditions were detected and no condition-by-group interactions were found, which suggests that the decreased functional connectivity in amusia persisted irrespective of which acoustic cues judgments were based on. In addition, no differences in activity level were detected between the groups or conditions, and task performance levels, age, and degree of head motion were equivalent in the two groups. We suggest, therefore, that the reduced reliance on pitch exhibited by individuals with amusia during speech perception is in reduced connectivity between language and pitch processing areas. Implications for other neurological conditions are discussed.

Disclosures: K. Jasmin: None. **F. Dick:** None. **L. Stewart:** None. **L.L. Holt:** None. **A. Tierney:** None.

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Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.08

Topic: A.09. Adolescent Development

Support: HFSP-CDF fellowship 2015
NIH-NINDS
WPI-IRCN (JSPS)
NIMH Silvio Conte Center (P50MH094271)
Giovanni Armenise Foundation
NVIDIA Corporation

Title: Deep learning detection of early cholinergic impairments by spontaneous arousal fluctuations in autism

Authors: *P. ARTONI[1], A. PIFFER[1], V. VINCI[1], J. LE BLANC[1], C. A. NELSON[2], T. K. HENSCH[3], M. FAGIOLINI[1];
[1]Neurobio. Dept., Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [2]Departments of

Pediatrics and Neurosci., Harvard Med. Sch., Boston, MA; [3]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA

Abstract: Neurodevelopmental disorders are typically diagnosed (e.g. autism at 4 years old) beyond the critical period for many sensory, perceptual and language functions. Translational, quantitative and non-invasive biomarkers for early diagnosis are urgently needed to spur intervention. As an indicator of internal dynamic neuromodulatory activity in the brain, spontaneous arousal fluctuations are easily detected by measuring time-series pupil size or heart rate variability. Here, we show that both idiopathic (BTBR) and monogenic (CDKL5- or MeCP2-deficient) mouse models of autism display early, aberrant arousal states linked to altered cholinergic signaling. In the MeCP2-deficient mouse model of Rett Syndrome, such arousal abnormalities were already detectable prior to regression and were reversed by the selective re-expression of MeCP2 in cholinergic neurons. To robustly detect subtle patterns, we trained a deep convolutional neural network (ConvNetACh) to recognize signatures of altered arousal fluctuations due to altered cholinergic tone. We used spontaneous pupil fluctuation data from LYNX1-deficient mice (carrying a deliberately enhanced nicotinic receptor sensitivity) and their wild-type littermates to train ConvNetACh, reaching 97% accuracy. This in turn successfully detected impairments across all autism mouse models tested except in those MeCP2-deficient mice wherein the cholinergic circuit had been rescued. Moreover, a selective re-training of only the last layers of the mouse ConvNetACh using heart rate fluctuations collected in Rett Syndrome patients (where steady eye gaze is difficult to obtain), generated a neural network (ConvNetPatients) capable of distinguishing them from typically developing subjects. Our transfer learning study is the first across species and modalities, exhibiting significant accuracy even with a small cohort of rare patients, reaching 80% correct between the first and second year of life, and up to 88% in stage III patients. Together, these results indicate that distinct autism models share early onset arousal abnormalities reflecting altered cholinergic circuitry. Probing spontaneous arousal fluctuations as a proxy with deep learning represents a new tool for their early detection and potential intervention.

Disclosures: P. Artoni: None. **A. Piffer:** None. **V. Vinci:** None. **J. Le Blanc:** None. **C.A. Nelson:** None. **T.K. Hensch:** None. **M. Fagiolini:** None.

Nanosymposium

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Presentation Number: 726.09

Topic: A.09. Adolescent Development

Support: Grants-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science

The Strategic Research Program for Brain Sciences by the Japan Agency for Medical Research and Development
The Center of Innovation Program and Core Research for Evolutional Science and Technology from Japan Science and Technology Agency
Ministry of Education, Culture, Sports, Science and Technology

Title: Are we there yet? Classifying individuals with autism and schizophrenia based on brain neuroimaging data using multiple machine learning algorithms

Authors: *W. YASSIN[1], Y. ZHU[2], H. NAKATANI[2], M. KOJIMA[1], K. OWADA[1], H. KUWABARA[8], N. OKADA[3,4], W. GONOI[5], H. TAKAO[5], K. KASAI[3,4,6,7], Y. KANO[1,6], O. ABE[5], H. YAMASUE[8], S. KOIKE[4,2,6,7];
[1]Dept. of Child Neuropsychiatry, [2]Ctr. for Evolutionary Cognitive Sci., [3]Dept. of Neuropsychiatry, [4]Intl. Res. Ctr. for Neurointelligence (IRCN), [5]Dept. of Radiology, [6]Univ. of Tokyo Inst. for Diversity & Adaptation of Human Mind (UTIDAHM), [7]Ctr. for Integrative Sci. of Human Behavior, The Univ. of Tokyo, Tokyo, Japan; [8]Dept. of Psychiatry, Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan

Abstract: Introduction: Proper diagnoses can save lives. In order to be given a diagnosis, individuals with mental illness have to fit a certain diagnostic criterion based on manifested behavior. Some patients might slip through certain criteria yet still suffer from its debilitating symptoms. Advances in artificial intelligence might be able to provide support in catching these patients and identifying mental disorders based on several brain data, independent of the manifested behavior. Here we present a comparative approach between multiple machine learning algorithms classifying Individuals with autism spectrum disorder (ASD) and schizophrenia (Sch) based on various types of neuroimaging data.
Methods: Forty-five adults with ASD, 33 with Sch and 108 typically developing individuals (TD) participated in this study. Imaging was acquired using a 3T MRI scanner. Freesurfer was used to obtain the neuroanatomical data; subcortical volume (sCV), surface area (SA), and cortical thickness (CT). Data quality was assessed using ENIGMA. The machine learning classifiers, Logistic regression (LogReg), K -nearest neighbors (KNN), decision tree (DT), adaptive boosting (AdaB), random forests (RF), and support vector machines (SVC) were utilized to classify individuals with ASD, Sch and TD into their respective categories based solemnly on their neuroanatomical data, separately and combined.
Results: Each classifier showed a distinct accuracy in classifying ASD, Sch and TD individuals based on their neuroanatomical data. LogReg showed the highest accuracy using the CT data (69.57%), followed by sCV (54.35%) and SA (54.35%). KNN showed highest accuracy in both sCV (65.22%) and CT (65.22%), DT in sCV (67.39%), AdaB in CT (69.57%), RF in CT (69.57%) and SA (69.57%), and lastly SVC in SA (69.57%). The combined data (sCV, SA and CT), showed highest accuracy within all the following classifiers, KNN (67.39%), DT (67.39%), AdaB (69.57%), RF (69.57%) and SVC (71.74%). LogReg did not show such trend (67.39).
Conclusion: Cortical thickness seems to provide the highest accuracy in classifying individuals with ASD, Sch and those who are TD. Adaptive boosting produced the highest overall accuracy. Continued assessment and implementation of different classifiers are required to investigate neuropsychiatric disorders based on neuroimaging data.

Disclosures: **W. Yassin:** None. **Y. Zhu:** None. **H. Nakatani:** None. **M. Kojima:** None. **K. Owada:** None. **H. Kuwabara:** None. **N. Okada:** None. **W. Gonoi:** None. **H. Takao:** None. **K. Kasai:** None. **Y. Kano:** None. **O. Abe:** None. **H. Yamasue:** None. **S. Koike:** None.

Nanosymposium

726. Personalized Brain Signatures

Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.10

Topic: I.07. Data Analysis and Statistics

Title: The connectivity fingerprinting toolbox

Authors: ***D. E. OSHER**, Z. M. SAYGIN;
Psychology, The Ohio State Univ., Columbus, OH

Abstract: Since the advent of neuroimaging, there has been considerable interest in mapping the human brain. This has led to exquisite maps of neural selectivity, but mapping is a purely descriptive approach to understanding the brain. In order to uncover mechanistic explanations, rather than descriptive maps of the brain, neuroimagers will need to incorporate neural connectivity into their analyses. After all, connectivity is the principal constraint on the domain of information that a brain region can process, and thus should be highly predictive of neural selectivity. We previously showed that connectivity fingerprints can define a region so well that they can be used to predict the location and degree of neural activity in a brain region, even in the absence of functional localizers, using only an individual's connectivity patterns (Osher et al. 2015; Osher et al. 2018; Osher et al. 2019 in press). This technique is precise to the fine grain of a single voxel from a single individual. Here we present a suite of analytic tools that will allow researchers to derive the connectivity fingerprints that best define any specific brain region, offering answers to questions such as "what is the connectivity pattern that a voxel must have to be highly selective to faces?" and "what is the connectivity pattern that distinguishes different cortical regions, even within a functional network?" Our software suite is applicable to DWI as well as functional connectivity data, any set of brain regions as seeds and targets, any fMRI task, and any number of individuals. We also demonstrate how connectivity fingerprints can be used to predict behavioral data, in addition to neural activation in each subject. We present a few specific results from the application of connectivity fingerprints to predict neural activation in individual subjects and behavioral variation in various mental tasks, thus demonstrating the application of the connectivity fingerprinting method to develop parsimonious explanations of structure, function, and individual variation in behavior.

Disclosures: **D.E. Osher:** None. **Z.M. Saygin:** None.

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Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.11

Topic: I.07. Data Analysis and Statistics

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The National Key Research and Development Program of China (2016YFC1306300)
National Natural Science Foundation of China (Grant 61633018)
Beijing Municipal Commission of Health and Family Planning (PXM2019_026283_000002)

Title: 100% positive predictive value is achieved in a subset of individuals using a multi-step machine learning classification procedure to identify progression from mild cognitive impairment to Alzheimer's dementia

Authors: *D. A. DAWSON[1,2], Z. HAO[3,4], K. MOK[2], S. GREGOIRE[2], L. LIN[5], Y. HAN[5,6,7,8], P. BELLEC[9], A. SHMUEL[2,1];
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Abstract: Currently there are no clear methods for determining the prognosis of individuals presenting with Mild Cognitive Impairment (MCI). Early identification of those MCI who will progress to dementia may be possible with computational analysis of MRI images. We hypothesize that accurate classification of groups of individuals who progress from MCI to dementia (Progressor) and those who do not (Stable) can be achieved using fine scaled whole brain resting state functional connectivity, gray matter volume and cortical thickness. Given the heterogeneity of the MCI population and limited accuracy achieved in prior studies looking at all MCI together as one group, we apply a subtyping algorithm to the MRI measures. The data analyzed (3T RS-fMRI and T1-MRI) comes from the Alzheimer's Disease Neuroimaging Initiative (96 scans, 14 Progressors; 222 scans, 52 Stables), and Dr. Ying Han's lab at the XuanWu Hospital - Capital Medical University (Li et al., 2016) (39 scans, 32 Progressors; 43 scans, 21 Stables). Analyses were done on the whole brain with the HCP cortical parcellation combined with the Freesurfer subcortical segmentation. See Figure 1 for flow of analyses. Figure 2 shows the results of our top five analyses, each achieving 100% positive predictive value in one class. While each individual analysis only allows for confident classification in 1.5-12.7% of

scans (3.1-6.2% subjects), combined the results from these analyses allow for confident classification in 23% of scans (12.4% subjects).

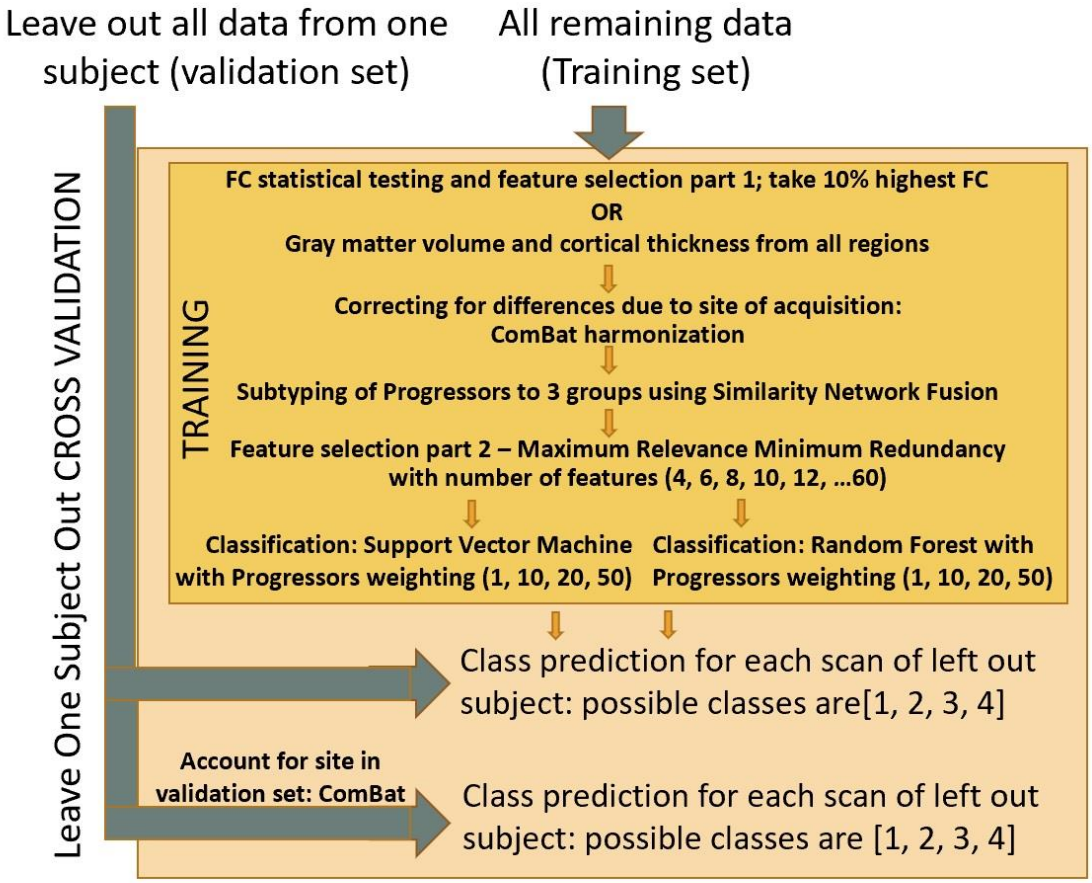

Figure 1. Methods workflow. We use a "leave one subject out" validation procedure in order to classify subjects as Stable (class 1) or Progressor (class 2, 3, 4). We assessed the functional connectivity (FC) differences between groups via general linear model. The FC in the lowest 10% of the p-value distribution or the gray matter volume and cortical thickness are used as possible features for use in Support Vector Machine or Random Forest classifiers. FC / gray matter volume and cortical thickness measures are submitted to the Maximum Relevance Minimum Redundancy feature selection algorithm. Finally, given that the site of the new data may not be accounted for in the training set, we consider correcting for site effects in the validation data via the ComBat harmonization method (Yu et al., Human Brain Mapping, 2018).

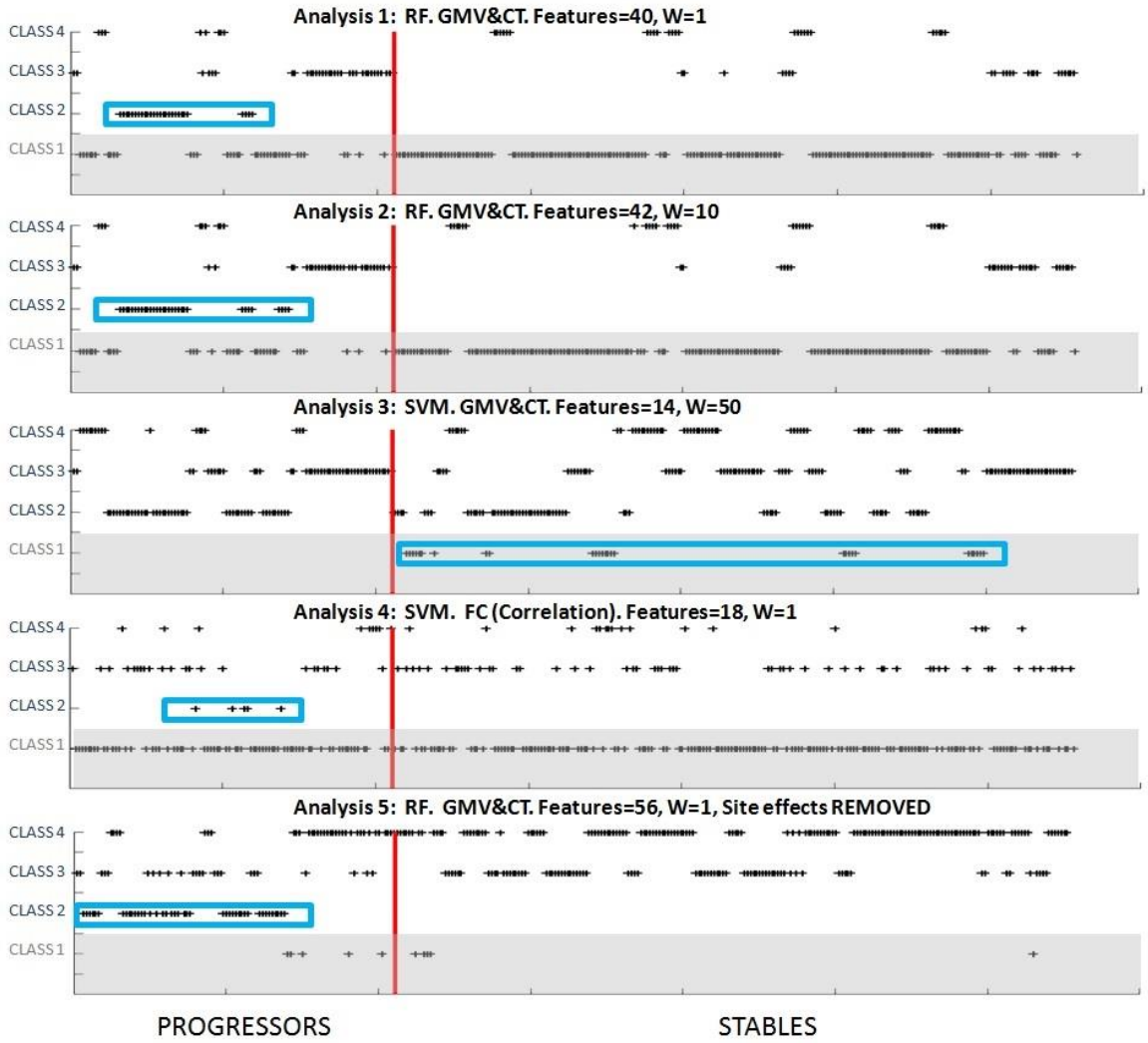

Figure 2. Classification results from the most successful classifiers with either gray matter volume and cortical thickness (GMV&CT) (Analyses 1-3, 5) or FC measures (correlation in this case, Analysis 4). Predicted class is represented on the vertical axis, with class 1 representing Stables (gray background), and classes 2, 3 and 4 representing Progressors (white background). Results boxed in blue are those with 100% positive predictive value for a specific class. Scans classified in an analysis are represented on the horizontal axis with Progressor scans on the left of the red vertical line, and stables on the right. "Site effects removed" (Analysis 5) indicates that, when the site of test data is accounted for in the training set, site effects are removed from test data. W is the weight parameter associated with progressor data during classifier building. For stable data weight is always 1. Number of features used in the classifier is indicated in the title of each panel. Results shown are from the best analysis within a range of consecutive analyses with different numbers of features with comparable results. Analysis 3 is comparable over 3 consecutive analyses, while GMV&CT analyses are comparable over 6 or more consecutive analyses.

Disclosures: D.A. Dawson: None. **Z. Hao:** None. **K. Mok:** None. **S. Gregoire:** None. **L. Lin:** None. **Y. Han:** None. **P. Bellec:** None. **A. Shmuel:** None.

Nanosymposium

726. Personalized Brain Signatures

Location: Room N426

Time: Wednesday, October 23, 2019, 1:00 PM - 4:00 PM

Presentation Number: 726.12

Topic: B.09. Network interactions

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NIH Grant R01 NS073601

Title: Cortical fingerprinting using cosine similarity of TMS-EEG evoked responses

Authors: *R. A. OZDEMIR[1], E. TADAYON[1], P. BOUCHER[5], H. SUN[2], W. GANGLBERGER[2], M. WESTOVER[2], A. PASCUAL-LEONE[6], E. SANTARNECCHI[3], M. SHAFI[4];
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Abstract: Transcranial magnetic stimulation (TMS) evokes a series of electro-cortical potentials (TEPs) that evolve in time and space as a function of the stimulation site, and thus can be used to assess a broad range of neurophysiological characteristics. Accumulating evidence shows that TEPs are reasonably reproducible within-individuals but highly variable between-individuals. Nevertheless, the majority of studies evaluate conventional metrics of the amplitudes extracted from space-averaged TEPs with latencies of specific peaks in the grand-average (across-subject) TEP. Such a substantial data reduction approach ignores the rich spatial-temporal specificity of TEPs, and discards crucial information that can be used to uniquely characterize individual subjects, and more importantly, develop perturbation-based biomarkers of cortical neurophysiology in clinical populations. Here, we computed a similarity metric (cosine similarity-SI) that utilizes all the spatial-temporal information available in TEPs to fingerprint individuals across identical TMS-EEG sessions one month apart. We delivered a total of 150 single-pulses of TMS to anatomically defined targets in dorsolateral-prefrontal (DLPFC), motor (M1) and parietal (IPL) cortices in the left hemisphere, and resting-state fMRI functionally defined parietal targets of dorsal attention (DAN) and default mode (DMN) networks in the right hemisphere in 24 participants. SI within targets (i.e., LDLPFC in visit-1 vs LDLPFC in visit-2) was significantly higher than the between-target SI (e.g. LDLPFC in visit-1 vs DAN in visit-2), demonstrating the specificity of TEPs between different target sites. Importantly, the SI metric applied to a single site was able to identify individual subjects on repeat sessions with almost 80% accuracy; by combining data collected by stimulating across multiple sites, >90% accuracy was obtained, suggesting that combination of electro-cortical responses from multiple cortical regions reveals unique information regarding the neurophysiological profile of an individual. Thus, our results demonstrate that whole-scalp spatio-temporal evolution of TMS perturbation

based brain responses represent an individually unique “fingerprint” of cortical electrophysiology, that could potentially serve as a useful tool in (1) tracking individual’s brain function longitudinally across the lifespan, (2) developing neurophysiological biomarkers of behavior and cognition, (3) identifying subjects with or at risk for neuropsychiatric diseases, and (4) providing an objective index of changes in cortical neurophysiology in response to an intervention.

Disclosures: R.A. Ozdemir: None. **E. Tadayon:** None. **P. Boucher:** None. **H. Sun:** None. **W. Ganglberger:** None. **M. Westover:** None. **A. Pascual-Leone:** None. **E. Santarnecchi:** None. **M. Shafi:** None.

Nanosymposium

727. Advances in Brain Imaging

Location: Room S404

Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.01

Topic: I.02. Systems Biology and Bioinformatics

Title: Improved estimation of functional architecture with the quantification of local power-law dynamics in the human brain

Authors: *C. J. STEELE[1,2], P.-L. BAZIN[2,3,4], N. SCHAWORONKOW[5], A. VILLRINGER[2,6], V. NIKULIN[2,7,8];
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Abstract: Background: Functional connectivity is the integrated representation of functional dynamics within the structural network of the brain. Non-invasive methods such as electroencephalography and functional magnetic resonance imaging (fMRI) are commonly used to infer connectivity by correlating signal timecourses obtained during rest. Unfortunately, correlational methods suffer from biases due to slowly decaying power law temporal autocorrelations that are ubiquitous in functional data. Such long-range temporal dependencies result in spurious correlations and inflated false positives when standard analyses are used. Here, we estimated power-law dynamics in thousands of individual timecourses using the scaling exponent (SE) computed through detrended fluctuation analysis (DFA) to a) measure intrinsic functional dynamics and b) quantify and correct biases in functional correlations in human fMRI. **Method:** DFA was used to compute SE in resting state fMRI from the Human Connectome Project to illustrate the topographical distribution (1200 samples, 7 window steps). For each

original timeseries we also generated 1000 surrogate signals (retained SE dynamics, shuffled phases in the frequency domain) and correlated them to determine the distribution of r-values expected by chance for all timeseries pairs. This null distribution was used to compute the r-value cutoff threshold at a 95% confidence interval. We then fit a 3d function relating SEs from all pairs to the corresponding r-value cutoff to determine the empirical SE-dependent threshold. **Results and Implications:** We found that SE exhibited a spatial distribution across the cortex strikingly similar to that of glucose metabolism from positron emission tomography and high SE overlapped with regions associated with the default mode network. Surrogate simulation revealed that SE increases across the physiologically-valid range resulted in an approximately exponential increase in the r-value cutoff threshold. Our findings indicate that functional dynamics are dependent on anatomical location, resulting in systematic biases in functional correlations. The proposed surrogate procedure can be used to determine the empirical thresholds necessary to reject potentially spurious correlations and correct functional connectivity analyses. Further research is necessary to determine what portions of functional connectivity are due to genuine physiological factors rather than the spurious effects of high SE.

Disclosures: C.J. Steele: None. **P. Bazin:** None. **N. Schaworonkow:** None. **A. Villringer:** None. **V. Nikulin:** None.

Nanosymposium

727. Advances in Brain Imaging

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Presentation Number: 727.02

Topic: I.02. Systems Biology and Bioinformatics

Support: European Research Council (ERC, GA802371)
NARSAD (Independent Investigator Grant to A.G., #25861)

Title: Network structure of the mouse brain connectome with voxel resolution

Authors: L. COLETTA[1], F. GATTO[1], B. BERNHARDT[2], ***A. GOZZI**[3];
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Abstract: Detailed investigations of the mouse brain connectome have shown that the mouse brain recapitulates global organizational principles similar to those observed in higher species, including the presence of specialized modules interlinked by highly-connected hub nodes, a configuration that enables both local processing and efficient systemic integration (Oh et al., 2014). However, prior investigations of the mouse connectome have typically relied on the use of regional parcellations, hence limiting the spatial resolution of connectional mapping, and

preventing a precise characterization of the network structure and hierarchical topography of the mouse connectome. Here we leveraged a novel data driven model of the mouse connectome (Knox et al., 2018), to provide a first-of-its-kind brain-wide description of the network structure and hierarchical topography of the mouse connectome with voxel-resolution. Specifically, we applied graph theoretical measures (Liska et al., 2015) and diffusion map embedding (Marguiles et al., 2014) to a down-sampled voxel-scale version of the mouse connectome, such to link specific network features to previously described characterization of the mouse functional connectome as measured with resting state fMRI (Liska et al., 2015). We show that the mouse brain contains a set of precisely localized, topologically segregable hub-like structures, with polymodal cortical areas (e.g. prefrontal cortex) and olfactory regions serving as primary sources of neural input to the rest of the brain, and thalamo-striatal areas configured as neural sinks. We also report that the voxel-wise connectome can be portioned into five large-scale communities that spatially recapitulate fMRI connectivity networks of the mouse brain, and that such modules are reciprocally inter-connected via a set of spatially-localized hypothalamic and neuromodulatory integrative nuclei. We also demonstrate that the mouse connectome is highly-resilient to random or targeted attacks, and highlight a critical role of structural hubs in maintaining network communicability. We finally describe a common hierarchical organization of the functional and structure cortical connectome, entailing two principal gradients spanning polymodal and unimodal cortices that reconstitute evolutionary-conserved organizational principles of the cerebral cortex in higher mammalian species. Collectively, these results advance our understanding of the connectional architecture of the mouse brain, and lay the foundation for targeted manipulations of the mouse connectome based on its network and topological properties.

Disclosures: **L. Coletta:** None. **F. Gatto:** None. **B. Bernhardt:** None. **A. Gozzi:** None.

Nanosymposium

727. Advances in Brain Imaging

Location: Room S404

Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.03

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH R01 AG 059874
R01 MH 116147
R56 AG 058854
ADRC P50-AG05142- pilot project 34.3
UK Biobank: This research has been conducted using the UK Biobank Resource under Application Number ‘11559’.

Title: Age associations with choroid-plexus calcification volumes defined by quantitative susceptibility mapping

Authors: *I. BA GARI, W. SURENTO, A. H. ZHU, P. M. THOMPSON, N. JAHANSHAD; Imaging Genet. Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Univ. of Southern California, Los Angeles, CA

Abstract: Recent studies have shown that the bilateral choroid plexus undergoes histopathological changes due to aging. Intracranial calcification may arise as a result of recovery from tissue infection, hemorrhage-related posttraumatic scarring, vascular pathologies, or congenital abnormalities. Physiological calcification of brain structures may occur even without apparent evidence of disease, and is observable alongside chronological aging in the central nervous system (CNS). Choroid plexus calcification (CPcal) may be an important biomarker for studying brain aging. Computed tomography (CT) imaging has been traditionally used to quantify intracranial calcifications, but MRI-derived quantitative susceptibility mapping (QSM) may provide a radiation-free alternative for studying CPcal in the context of aging. We extracted and quantified the volume of CPcal from QSM in a large cohort (n = 379; 201 female) of adults (aged 46 - 77 years) from the UK Biobank . Brain MRI data was acquired on a Siemens Skyra 3 T scanner with 32-channel head coil. QSM was derived from susceptibility weighted imaging DICOMs by using the Laplacian boundary value background filtering (Zhou, 2014) and Morphology Enabled Dipole Inversion (MEDI) method (Liu, 2017) . A mask of the lateral ventricles, extracted with FreeSurfer version 5.3, was overlaid on the QSM image to ensure the boundaries of the ChPs are in the cerebrospinal fluid. Next, the CPcal volume was extracted through image thresholding of the QSM. We found the CPcal volume is positively associated with age when covarying for sex, age-by-sex, and intracranial volume ($p = 4.9 \times 10^{-5}$). Although we found no significant age-by-sex interaction, when stratifying by sex, we found that women showed a much stronger relationship between age and CPcal ($p = 1 \times 10^{-4}$), while men showed borderline associations ($p = 0.047$). As a comparison, we tested age associations with the lateral ventricle volumes provided by the UK Biobank and found no significant association in this sample, suggesting that CPcal volume may be a more reliable biomarker for brain aging, particularly in women. The UK Biobank is a large dataset with scans of approximately 100,000 individuals planned. We plan to extend this pilot work to the larger dataset, and assess relationships with brain disease.

Disclosures: I. Ba Gari: None. **W. Surento:** None. **A.H. Zhu:** None. **P.M. Thompson:** None. **N. Jahanshad:** None.

Nanosymposium

727. Advances in Brain Imaging

Location: Room S404

Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.04

Topic: I.07. Data Analysis and Statistics

Support: NIDCD R00DC013828

Title: Building generalizable cognitive models using ECoG: An improvised technique for group-level analysis

Authors: *G. KARTHIKEYAN[1], A. M. BELTZ[1], D. BRANG[2];
[2]Psychology, [1]Univ. of Michigan, Ann Arbor, MI

Abstract: Non-invasive EEG recordings in humans often use parametric statistics to identify group-level differences between conditions by recording activity at the same electrodes in all participants. Research using electrocorticography (ECoG) has traditionally been unable to conduct parametric group analyses because of high variability in electrode locations across patients, as electrodes are placed according to the differing clinical needs of each patient. Attempting to overcome this limitation, prior studies used within-subject statistics at each individual electrode, and then projected results into a normalized anatomical space, reporting the number of significant and non-significant electrodes within areas of interest. While this method leverages the high SNR of ECoG at the single-subject level, it tends to not be useful for generalizing results across multiple participants or to the general population (for example, it is unclear how to interpret a region that includes 15 electrodes, of which 5 are highly significant and 10 are non-significant). Here we demonstrate the use of mixed-effects modelling with ECoG data to overcome this limitation, enabling more statistically robust group-level analyses. Our test dataset included high-gamma power filtered signals from auditory areas in a large cohort of patients (13 participants, 295 electrodes total) who completed a phoneme perception paradigm. Group-level analyses using mixed-effects modelling (random intercept = individual participant effects) were performed to identify the distribution and timing of phoneme activity at the group level. Analyses identified significant ($p<.05$, fdr-corrected) group-level activation of 76.9% of auditory vertices, with a minimum vertex-wise p-value of 2.3909e-286. The mixed-effects model remained sensitive to detecting activation in areas with few subjects or electrodes because of the high SNR of the ECoG signals. Preliminary analyses indicate that mixed-effects models are more sensitive to small effects than conventional ECoG analyses. Critically, this approach demonstrates the ability to build cognitive models using ECoG data that better generalize across participants and to the general population.

Disclosures: G. Karthikeyan: None. **A.M. Beltz:** None. **D. Brang:** None.

Nanosymposium

727. Advances in Brain Imaging

Location: Room S404

Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.05

Topic: I.07. Data Analysis and Statistics

Support: NIH/NIBIB (P41-EB018783)
NIH/NIBIB (R01-EB026439)
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NIH/NINDS (U01-NS108916)
NIH/NICHD (R25-HD088157)
NIH/NIMH (P50-MH109429)
US Army Research Office (W911NF-14-1-0440)

Title: Passive mapping of receptive language area in patients under general anesthesia using electrocorticography

Authors: *A. NOURMOHAMMADI[1], A. DE PESTERS[2], P. BRUNNER[3], J. KNUTH[4], A. RITACCIO[5], G. SCHALK[6];
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Abstract: Resective brain surgery is often necessary with specific neurological disorders such as intractable epilepsy or brain tumors. Since pathological brain tissue can be situated in close proximity or within eloquent cortex, it is crucial to obtain an accurate functional map of the brain so that resection can maximally remove pathological tissue without impacting eloquent areas. While imaging techniques such as fMRI have shown to provide valuable information about the functional significance of different cortical regions, the gold standard for intraoperative mapping remains direct cortical stimulation (DCS) of the cortex. However, when applied to language mapping, DCS has several limitations, including the requirement of an awake and cooperating patient. Together, these limitations impose a limit on the number of neurosurgical patients that can benefit from this technique.
Several studies have shown that passive mapping using electrocorticographic (ECoG) signals is effective for localizing function, can do so rapidly and safely, and its results are in substantial congruence to those derived using DCS. At the same time, up to the present, ECoG-based functional mapping of language function still required an awake and cooperating patient, and thus could not be applied in patients under general anesthesia.
In this study, we hypothesized that it is possible to perform ECoG-based functional mapping in patients under general anesthesia, and that the results are in general congruence to similar results achieved when the same patients are awake. To test this hypothesis, we presented speech stimuli to 10 epilepsy and 8 tumor patients while they were awake and fully anesthetized. We then derived broadband gamma ECoG responses during the awake and anesthesia conditions to delineate receptive language areas. The results show that in all subjects, passive mapping identified areas on or close to superior temporal gyrus during both the awake as well as the anesthesia conditions. Compared to the mapping results in the awake patients, the results for the anesthesia condition had a sensitivity of 46 percent and a specificity of 99 percent.
Our findings to date demonstrate the feasibility of mapping receptive language functions in

anesthetized patients. With further validation and optimization of the anesthesia protocol, we expect that the ability to functionally map patients during anesthesia will increase the number of people that can benefit from this technique.

Disclosures: A. Nourmohammadi: None. **A. De Pesters:** None. **P. Brunner:** None. **J. Knuth:** None. **A. Ritaccio:** None. **G. Schalk:** None.

Nanosymposium

727. Advances in Brain Imaging

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Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.06

Topic: B.09. Network interactions

Title: Electric fields between 1 and 10 $^{mV}/_{mm}$ induce immediate electrophysiological effects in humans

Authors: E. ZEYKINA[1], M. MITTNER[2], W. PAULUS[1], ***Z. TURI**[1];
[1]Univ. Med. Ctr. Goettingen, Goettingen, Germany; [2]Inst. for Psychology, Univ. of Tromsø, Tromso, Norway

Abstract: Neurons do not only produce oscillating electric fields (EFs), they also respond to both endogenous and exogenous EFs. This holds a promise for employing non-invasive electrical brain stimulation methods, such as repetitive transcranial magnetic stimulation (rTMS) to modulate endogenous network oscillations. The two crucial properties of rTMS are its frequency and its magnitude. Whereas the frequency of the EF is clearly defined, the vast majority of rTMS studies select the stimulator output rather than the resulting EF magnitudes. These two quantities can differ significantly because of anatomical differences. This is a crucial limitation, because it is the EF magnitude that purportedly governs the underlying neural mechanisms and functional effects of rTMS. Here, we propose and successfully implement an alternative approach, where prospective computational modeling of the resulting EF guided the choice of stimulation intensity at the single subject level and individual peak frequency estimation of the posterior alpha frequency band fine-tuned the choice of stimulation frequency. Our study employed a single-blind, randomized, cross-over design. Each participant (n=16; 8 female; mean age 25.5 yrs) received rhythmic (main) and arrhythmic (control) rTMS protocols. The stimulation was applied at 3 different EF doses - 5, 10 and 15 $^{mV}/_{mm}$ corresponding to the peak EFs of the normal component in the target region. In the exploratory analysis, we find that rhythmic but not arrhythmic rTMS increases the amount of synchronization in the alpha-frequency band as recorded with simultaneous electroencephalography during rTMS. We observed this effect already at the lowest rTMS intensity, 5 $^{mV}/_{mm}$, which is 5-times lower than typically used by conventional dosing. A region of interest (ROI) analysis focusing on the mean EF shows that EF magnitudes were above $1^{mV}/_{mm}$ EF in the target hemisphere: Previous in-vitro and in-vivo animal

studies have shown that this EF intensity is effective for temporally biasing spikes and for inducing neural entrainment in network oscillations. Bayesian hierarchical regression analysis suggest that the amount of synchronization in the posterior electrodes is the highest if the EF magnitude is ~ at 10 $^{mV}/_{mm}$ and lower if it is below or above this intensity. These results suggest that we can induce immediate electrophysiological effects in humans using 5-times lower EF magnitudes for rTMS, when compared to the lowest conventional dosing (80% of resting motor threshold). We propose that rTMS at conventional dosing uses much higher EF magnitudes then necessary for temporally biasing spike activity or for inducing neural entrainment in humans.

Disclosures: E. Zeykina: None. **M. Mittner:** None. **W. Paulus:** None. **Z. Turi:** None.

Nanosymposium

727. Advances in Brain Imaging

Location: Room S404

Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.07

Topic: I.07. Data Analysis and Statistics

Title: Using electrocardiography (ECG) to discern brain state and dysfunction

Authors: *A. M. JONES[1], B. R. SHETH[2];
[1]Neurosci., USC, Los Angeles, CA; [2]Dept Elec, Comp Eng, Univ. of Houston, Houston, TX

Abstract: Our work explores the strength of the communication between the brain, i.e., the central nervous system, and the autonomic nervous system. Principally, we focus on using the electrocardiogram (ECG/EKG), which reflects autonomic activity and is a robust, easy-to-record signal, to yield information about the short-term state and long-term condition of the brain. Along these lines, we recently demonstrated an algorithm that uses single-channel ECG data alone to automatically score all five stages of sleep (W/S1/S2/SWS/REM) at an expert-level of agreement (Cohen's $\kappa = 0.71$, Fig. 1) with clinically-recorded, "gold standard" polysomnography (PSG) on thousands of subjects aged 5 to 95. Having thus substantiated the utility of ECG as a window into brain states, we are leveraging the same methods to probe ECG for additional markers of brain activity and mental health. Initial tests have led us to further investigate the following: **1)** On the topic of sleep, possible correlates of characteristic features of sleep, e.g., spindles, K-complexes, and large delta waves; moreover, it stands to reason other similar electroencephalography (EEG) features, for instance, prominent oscillations and entrainment of multiple frequencies, may also have ECG signatures. **2)** On the topic of dysfunction, possible signs during sleep of brain diseases and disorders such as Alzheimer's, Parkinson's, and depression; because ECG is cheaper and less intrusive than current neuro-electrophysiological techniques, e.g., PSG, it would be invaluable to apply ECG to the early detection of brain dysfunction—alone, or in conjunction with neuropsychological tests. Our studies so far have expanded upon what is possible to ascertain conclusively about brain state with ECG. With these

new methods, further research into the autonomic correlates of brain activity and mental health will likely produce new diagnostic tools and insights into the communication between brain and body.

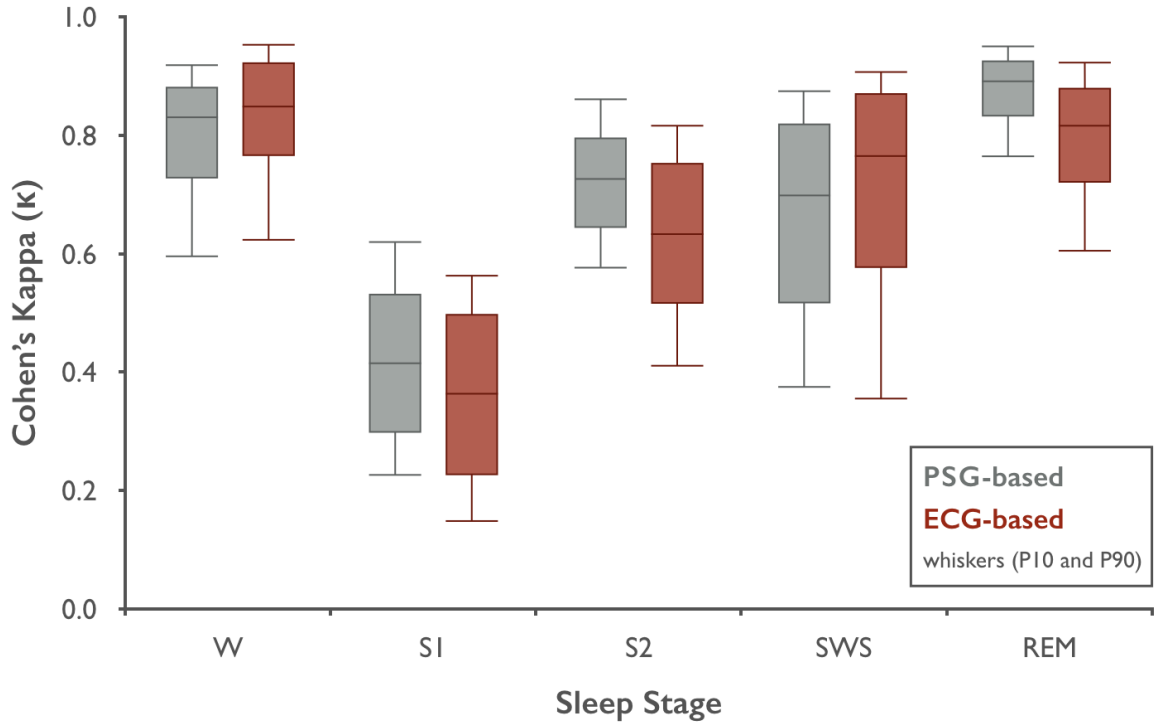

Fig. 1. A comparison of PSG (gray) based manual scoring and our algorithm (red) using R&K. Adapted with permission from Danker-Hopfe et al. (2009).

Disclosures: **A.M. Jones:** None. **B.R. Sheth:** None.

Nanosymposium

727. Advances in Brain Imaging

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Presentation Number: 727.08

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant MH106520

Title: Accounting for test-retest reliability and power to design better GABA-edited magnetic resonance spectroscopy studies

Authors: *T. KOLODNY[1], M.-P. SCHALLMO[3], R. A. E. EDDEN[4], R. BERNIER[2], S. O. MURRAY[1];
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Abstract: γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. It plays a key role in maintaining neuronal excitation/inhibition balance in the heathy brain, and its dysfunction has been implicated in various neurological and psychiatric disorders, including autism spectrum disorders, schizophrenia, depression and anxiety. Methodological advances in spectral editing of MR spectroscopy (MRS) in the past decade provide accessible protocols for quantification of GABA *in vivo*. However, the reproducibility and reliability of these measurements is a concern.
To assess test-retest reliability of GABA measurements, we obtained MRS data from the visual cortex in a large sample of young healthy adult participants (N=39; 22 males; ages 18-30). Data were acquired using MEGA-PRESS spectral editing, in a midline occipital volume of interest (3 cm isotropic voxel), centered bilaterally on the calcarine sulcus, in two different scanning sessions up to 14 days apart. We computed the intra-class correlation coefficient (ICC = .19) and the intraindividual coefficient of variation (ICV = 4.3%) as estimates of reliability.
We then use the obtained reliability estimates to calculate power and required sample size to detect a range of possible effect sizes for three types of experimental designs: (1) within-subjects designs that modulate GABA concentration by experimental manipulation; (2) individual differences designs that examine correlations between GABA concentration and other measures such as behavior, self-report questionnaire data, or other neuroimaging data; (3) between-subjects designs that compare GABA concentration between clinical and control groups.
Our results demonstrate how accounting for empirical MRS measurement reliability greatly impacts power estimation, and indicate that sample sizes typically used in the MRS literature suffer from a severe lack of power, raising questions about results and interpretation. We further use the simulations to evaluate feasibility of various study designs, and to formulate recommendations for planning future MRS experiments, utilizing repetition of MRS scans within-subjects and sufficient sample sizes to overcome low measurement reliability.

Disclosures: T. Kolodny: None. **M. Schallmo:** None. **R.A.E. Edden:** None. **R. Bernier:** None. **S.O. Murray:** None.

Nanosymposium

727. Advances in Brain Imaging

Location: Room S404

Time: Wednesday, October 23, 2019, 1:00 PM - 3:15 PM

Presentation Number: 727.09

Topic: I.02. Systems Biology and Bioinformatics

Support: DA044015

Title: Utilizing electronic health records to study brain disorders

Authors: *V. TROIANI, A. ROY, D. BEILER;
Geisinger, Lewisburg, PA

Abstract: Neuroimaging has been used for decades to study the brain-related changes associated with neurological, neurodevelopmental, and psychiatric disorders. Patients are traditionally recruited for research participation and prospectively complete a series of brain MRIs along with behavioral assessments. As we have entered the era of 'big data', large scale endeavors such as the Autism Brain Imaging Data-sharing Initiative (ABIDE) have implemented extensive recruitment for MRI projects of specific disease groups. These efforts are a great resource, but are associated with high cost and bias subject recruitment towards those that seek-out research participation. One cost-efficient resource that is gaining traction as a data-driven method for the study of various medical conditions is electronic health record (EHR) data mining. We assess the number of patients that complete structural MRIs in the context of standard clinical care and whether these images can be used to study a variety of brain disease processes (i.e. healthy aging, substance abuse disorder, etc.). We do this within an integrated healthcare system, Geisinger, which delivers primary and specialty care to 3 million patients in central Pennsylvania. A pipeline was first developed to extract MRI studies from a clinical picture archiving system (PACS) into a completely deidentified research PACS through a data broker process. Phenotype data from the EHR of patients that completed an MRI study, including longitudinal diagnoses and radiology reports, are then deidentified and imported into a Redcap database. Images are then curated to flag 'normal' MRI's as well as filtered based on diseases known to impact the brain (brain cancer, aneurism, stroke) using International Statistical Classification of Disease (ICD) Codes and automated text search of the radiology reports. In ongoing validation procedures, we will assess reliability of VBM across patients with repeated imaging data as well as confirm known findings of gray matter atrophy that occur with normal aging. In sum, we show that MRI data extracted from clinical records can be successfully analyzed using adapted analytic pipelines and then combined with an unlimited range of clinical diagnoses, including brain disorders and comorbidities.
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Disclosures: V. Troiani: None. **A. Roy:** None. **D. Beiler:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.01

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Prior support from MH068012,
MH057153,
NS11555,
and N00014-90-J-1490 from ONR.

Title: Do biological neural networks perform identifiable and verifiable canonical computations?

Authors: *D. GARDNER;
Dept. of Physiol. and Lab. of Neuroinformatics, Joan and Sanford I Weill Med. Col. of Cornell Univ., New York, NY

Abstract: At SfN 2018, I used the 25th anniversary of *The Neurobiology of Neural Networks* (Gardner 1993) to review advances in both biological neural networks (BNNs) and artificial nets (ANNs) that extended parallels and possibilities linking them.
However, in spite of the many individual successes of computational neuroscience, we incompletely understand the core, general, principle-how neuronal circuits compute, and what algorithms they use to do so: 1) What are the computations that BNNs perform to process sensory information, make choices, form memories, and plan and execute actions? 2) How do the networks learn these computations: how are they assembled, rewired or pruned, and tuned, to reach the functional state capable of such computational processing? 3) Do the transformations or computations performed by BNNs form a small canonical set? 4) Which properties of nervous systems are neuromorphically essential for these computations? The first two questions ask how molecular, cellular, synaptic, and network properties give rise to the information processing necessary for neural computation. The third asks if evolution has converged on a small set of functions as it has on the components: neurons, glia, synapses, transmitters, etc. Such computations may be optimized for features of the real world such as locality, low-dimensionality, and relevance. The fourth question seeks to understand which specific properties of neurons, synapses, and networks enable computation. Neurons rely on many structures and processes, but although mitochondria, clathrin-mediated endocytosis, and Na/K ATPase may be essential, they are unlikely to mediate algorithmic computations.
Canonical mechanism candidates, common to all nervous systems, include: irregular firing, spikes and graded potentials, extensive fan-in/out, local nets with distant links. Specific connectivity, neuron type, E/I balance, etc. vary widely across nervous systems, so none of these are required for canonical computation.
Also at SfN 2018, I reviewed possibilities for neurobiological credit assignment: using global states, conditions, or errors to adjust specific, local synaptic strengths. I now note that nervous systems need to solve *two* credit assignment problems: the first is developmentally and experentially tuning very many parameters other than synaptic strength; the second is the conventional synaptic strength tuning during learning.
Identifying canonical computations and mechanisms, or alternatively showing that these vary widely and that there is no single principle, will require extensive work by multi-investigator collaborative groups.

Disclosures: D. Gardner: None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.02

Topic: I.06. Computation/ Modeling/ and Simulation

Support: ONR N00014-16-2327
NIH R01 EB022891

Title: A model cortical circuit capable of temporal sequence learning and recall

Authors: *I. CONE[1,2], H. Z. SHOUVAL[1];
[1]Neurobio. and Anat., Univ. of Texas Med. Sch. at Houston, Houston, TX; [2]Applied Physics, Rice Univ., Houston, TX

Abstract: Sequence representation is an essential part of many kinds of learning and memory, and as such there may be common design principles which describe the circuits that mediate it. This work proposes a substrate for such representations, via a biophysically realistic network model that can robustly learn and recall sequences of variable order and duration. Our model network is in agreement with recent experimental results, which have shown that visual temporal sequence representations may be stored and recalled by local neural circuits in visual cortex. While this model is designed specifically to account for these observations in V1, it can also be thought of as a general circuit model for sequence representation, regardless of cortical modality. The model consists of a network of spiking leaky-integrate-and-fire model neurons placed in a modular architecture designed to mimic cortical microcolumns. This network is stimulated from an input layer designed to mimic LGN inputs. Learning is performed via competitive LTP and LTD like “eligibility traces”, which hold a history of synaptic activity before being converted into changes in synaptic strength upon the presentation of reward. This short term synaptic history solves the temporal credit assignment problem that arises from traditional Hebbian rules. A recent study has found evidence that these eligibility traces indeed exist and are consistent with the theoretically proposed mechanism that can be used to associate distal events. Before training, the network only produces naïve responses to incoming stimuli, and contains no memory of any particular sequence. During training, a particular temporal sequence of visual stimuli is repeatedly presented to the network. After training, presentation of only the first element in that sequence is sufficient for the network to recall its entire learned representation of the sequence. This capability suggests the network provides a possible framework for biologically realistic sequence learning and memory.

Disclosures: I. Cone: None. **H.Z. Shouval:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.03

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant R01-NS101356
CNPq Science without Borders Scholarship 203059/2014-0
Larry Deaven Ph.D. Fellowship in Biomedical Sciences

Title: Evaluating the contributions of individual sites of neuronal plasticity to an engram

Authors: *R. M. COSTA[1], D. A. BAXTER[2], J. H. BYRNE[1];
[1]Neurobio. and Anat., The Univ. of Texas Hlth. Sci. Ctr. At Houston, Houston, TX; [2]Engin. & Med., Texas A&M Hlth. Sci. Ctr., Houston, TX

Abstract: The frequency, regularity and selection of feeding behavior in *Aplysia* can be modified by operant reward learning (Brembs et al., 2002; Nargeot et al., 2007). Several neuronal correlates of this form of learning have been identified, including increases in the excitability of B30, B51, B63 and B65, and increases in the electrical coupling among B30, B63, and B65 (Brembs et al., 2002; Nargeot et al., 1999a,b, 2009). These four cells are part of a central pattern generator (CPG) that produces buccal motor patterns (BMPs), which can be segregated into two broad categories, those mediating ingestion (iBMPs) and those mediating rejection (rBMPs). To examine the ways in which individual sites of plasticity contribute to, and thus are assigned credit for, increases in the frequency, regularity and bias toward iBMPs, a model of the CPG was developed. The current model is an extension of the one developed by Cataldo et al. (2006), and was implemented using the neurosimulator SNNAP (Ziv et al., 1994). The current model includes conductance-based descriptions of cells CBI-2, B4, B8, B20, B30, B31, B34, B40, B51, B52, B63, B64, and B65, as well as their chemical and electrical synapses. Increasing the coupling among B30, B63, and B65 increased the regularity of BMPs, but did not increase their frequency nor bias CPG activity toward iBMPs. Increasing the excitability of B30, B63, and B65 increased the regularity and frequency of BMPs, but did not bias activity toward iBMPs. Increasing the excitability of B51 increased the regularity of BMPs, biased activity toward iBMPs, but did not increase the frequency of BMPs. Combined increases in frequency, regularity, and bias toward iBMPs could only be obtained by simultaneously implementing all known sites of plasticity. Moreover, analyses of activity maps, which plotted activity in all cells, indicated that learning-induced plasticity altered activity in all thirteen cells. These results indicated that learning reconfigured the activity map and that this reconfiguration emerged from synergistic interactions among the multiple loci of plasticity that constitute the engram. This reconfiguration strategy may present a general mechanism by which nervous systems solve the credit assignment problem; i.e., assigning ‘credit’ for reward to specific sites of plasticity. Additional insights into the principles underlying implementation of the engram will require

further expansion of the model by including other known elements of the CPG, as well as experimental data on learning-induced changes throughout the CPG.

Disclosures: R.M. Costa: None. **D.A. Baxter:** None. **J.H. Byrne:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.04

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant HD071978

Title: Adaptation of human grip and load forces to load and texture during object manipulation

Authors: *E. P. GARDNER[1], C. TYMMS[3], S. BILALOGLU[2], Y. LU[4], P. RAGHAVAN[5]; [1]Neurosci. & Physiol., [2]Rehabil. Med., New York Univ. Sch. of Med., New York, NY; [3]Computer Sci., New York Univ., New York, NY; [4]Applied Statistics, Social Sci. and Humanities, NYU Steinhardt, New York, NY; [5]Rehabil. Med., New York Univ. Langone Med. Ctr., New York, NY

Abstract: Humans and non-human primates are distinguished from lower species by their ability to grasp objects with one hand, use their hands to modify their environment, and manufacture hand-held tools. Grasping an object requires coordination of tactile perception with fine motor skills. The grip force must be optimized to prevent excessive squeezing of the object (wasted force and/or object damage) or slippage of the object from grasp due to insufficient, weak forces. Humans typically estimate object mass, compliance and texture from previous experience, and use these predictions when grasping an object for the first time. To optimize performance, the applied forces are modulated by tactile signals from the hand during grasping. We tested these hypotheses using a precision grasp and lift task in healthy young adult subjects. In this study we used 3D printing to create objects with parametrically specified textured surfaces, and interfaced them with a precision grip instrument to measure grip and load forces while subjects performed a skilled grasp and lift task. Here we show how surface texture dimensions — texton spacing or wavelength (0.75-1.25 mm) and texton diameter (0.1-0.5 mm) — modulate grip force rates, magnitudes and timing, and interact with object load in healthy young adult human subjects. Loads of 250, 450 and 650 g were tested with each combination of texton diameter and wavelength. These skills require independent finger movements and the ability to flexibly adapt one's fingertip forces according to the surface texture, solidity, and weight of objects, and execute the grasp reliably. The load parameters exerted significant effects (p<0.0001) on both grip and load forces (peak and mean amplitudes and rates), but the texton diameter and wavelength and dimensions modulated only the grip force magnitude and rate. The analyses also

revealed significant interactions between texton dimensions, and object weight in predicting grip force parameters. These factors may reflect the size and spacing of tactile mechanoreceptors responsible for decoding spatial texture information from the fingertips, and force modulation attributable to hand motor function. The data suggest that the somatosensory system multiplexes more than one stimulus attribute as a testable, general, principle of sensory processing.

Disclosures: E.P. Gardner: None. **C. Tymms:** None. **S. Bilaloglu:** None. **Y. Lu:** None. **P. Raghavan:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.05

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Univ. of Sussex Sch. of Life Sci. PhD studentship
Univ. of Sussex Research Development Fund
BBSRC BB/P00766X/1

Title: Using closed-loop model optimisation to achieve specific, accurate neuron models

Authors: *F. B. KERN[1], R. LEVI[3], G. KEMENES[1], T. NOWOTNY[2];
[1]Sussex Neuroscience, Sch. of Life Sci., [2]Sussex Neuroscience, Dept. of Informatics, Univ. of Sussex, Brighton, United Kingdom; [3]Escuela politechnica Superior, Univ. Autonoma De Madrid, Madrid, Spain

Abstract: Models of ionic conductances have been used to describe the membrane potential of neurons with great success. The basic premise and appeal of the Hodgkin-Huxley formalism and related neuron models is that each modelled conductance maps directly onto an ion channel type. Thus, when a model is created and tuned to match a particular dataset, the expectation is that the model constitutes a veridical representation of the set of ion channels present in the corresponding neuron type. Furthermore, tuning a model typically requires a large amount of data, including data that can only be gathered by destructive pharmacological intervention. Modellers therefore combine data from many individual cells of a given type, tacitly assuming that they are identical in the modelled properties, and that existing individual differences are negligible or irrelevant.
However, on the one hand, substantial differences in channel expression and morphology have been observed even within populations of cells with comparable response properties. On the other hand, the model structures we use are potentially degenerate and can produce indistinguishable behaviour from many disparate parameter sets. While this property aids the model tuning process, it follows that few models are, in fact, veridical representations of the

neurons they describe. This presents a major problem when a model is to be used to predict responses to novel stimuli or interventions. By merely mapping a limited and multiply realisable input/output relationship, such models often fail to reflect the underlying properties and computations they explicitly refer to.
Here, we present a novel, closed-loop method of model optimisation in an attempt to address these issues. Harnessing GPU-enhanced parallel computation, we optimise models online, fitting against live data from a single neuron and thus avoiding the problem of individual variability. Further, we use stimuli that are maximally informative, tuning them in a closed-loop fashion either to provide information about specific functional properties of the neuron, or to elicit responses that our model candidates do not yet predict well enough. By actively probing for responses that require unique parameter combinations, we thus gain greater confidence that the resulting model is an accurate description of the computations performed by the target neuron. Finally, since optimisation is rapid and non-destructive, our approach allows us to study the relationship between cellular properties and circuit-level dynamics and thus opens the door to investigating how cellular processes such as homoeostasis and intrinsic plasticity enable robust function of brain circuits.

Disclosures: **F.B. Kern:** None. **G. Kemenes:** None. **T. Nowotny:** None. **R. Levi:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.06

Topic: I.06. Computation/ Modeling/ and Simulation

Support: EY12124

Title: A trafficking model for the pull-push neuromodulation of hebbian synaptic plasticity

Authors: *A. KIRKWOOD[1], S. MIHALAS[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Neuromodulation can profoundly impact the gain and polarity of postsynaptic changes in Hebbian synaptic plasticity. An emerging pattern observed in multiple central synapses is a pull-push type of control in which activation receptors coupled to the G-protein Gs promote long-term potentiation (LTP) at the expense of long-term depression (LTD), whereas receptors coupled to Gq promote LTD at the expense of LTP. Notably co-activation of both Gs- and Gq-coupled receptors enhances the gain both LTP and LTD. To account for these observations we propose a simple kinetic model in which AMPAR are trafficked between multiple subcompartments in and around the postsynaptic spine. In the model AMPAR in the postsynaptic density compartment (PSD) are the primary contributors to synaptic conductance. During LTP

induction AMPAR are trafficked to the PDS primarily from a small periPSD compartment. Gs-coupled receptors promote LTP by replenishing periPSD through increased AMPAR exocytosis from a pool of endocytic AMPAR. During LTD induction AMPAR are trafficked in the reverse direction, from the PSD to the periPSD compartment, and Gq-coupled receptors promote LTD by clearing the periPSD through increased AMPAR endocytosis. We claim that the model not only captures essential features of the pull-push neuromodulation of synaptic plasticity, but it is also consistent with other actions of neuromodulators observed in slice experiments and is compatible with the current understanding of the AMPAR trafficking.

Disclosures: A. Kirkwood: None. **S. Mihalas:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.07

Topic: I.06. Computation/ Modeling/ and Simulation

Support: MSCA Grant (fellowship) 794273
FWO fellowship 12L5115N

Title: Non-linear neural dynamics of a mutual inhibition circuit in a real-life/computer model hybrid system

Authors: *N. KOGO[1], F. B. KERN[2], T. NOWOTNY[2], T. AIHARA[3], R. VAN EE[1], R. VAN WEZEL[1];
[1]Biophysics, Radboud University, Donders Inst. For Brain, Cognition and Behaviour, Nijmegen, Netherlands; [2]Sussex Neurosci., Univ. of Sussex, Brighton, United Kingdom; [3]Tamagawa Univ., Tokyo, Japan

Abstract: Resolving conflicting cues is essential for brain function, e.g. establishing coherent visual perception from ambiguous and noisy input signals in decision-making processes. The balance between excitatory signals from coherent input and inhibitory signals from conflicting inputs must constitute the neural mechanism of competition involved in the process. To realize the neural competition there have been numerous computational models that implemented a mutual inhibition circuit (Fig. 1A). We investigated the dynamics of the mutual inhibition circuit by performing double patch clamp recording from two pyramidal neurons in layer II/III of mice visual cortex in vitro, combined with a novel dynamic clamp system to connect the two neurons. By implementing model inhibitory neurons and excitatory and inhibitory synapses, a mutual inhibition circuit between the two pyramidal neurons was established (Fig. 1B). By injecting depolarization currents to both neurons simultaneously we found that the two neurons start to generate bi-stable activity with alternating dominance between them (Fig. 1C). The neurons,

when dominant, showed slow progression of adaptation, and, when suppressed, showed slow ramp-like depolarization because of the recovery of adaptation and decreasing drive of inhibitory inputs. When the model synaptic strength was set low, the reversal of dominance was interleaved with a transition phase where both neurons were active while when the strength was set high, the reversal occurred at once. We found that the temporal dynamics of the bi-stability was also dependent on noise. The variation of dominance durations correlated with the variation of the time course of the pyramidal neurons' adaptation. Furthermore, addition of simulated synaptic noise caused faster reversals (Fig. 1D).
It is possible that the mutual inhibition circuit works as a canonical component of neural machinery and is involved in a wide range of signal processing in the brain. The data we report here shed light on the fundamental role of the circuit in the dynamic properties of signal processing.

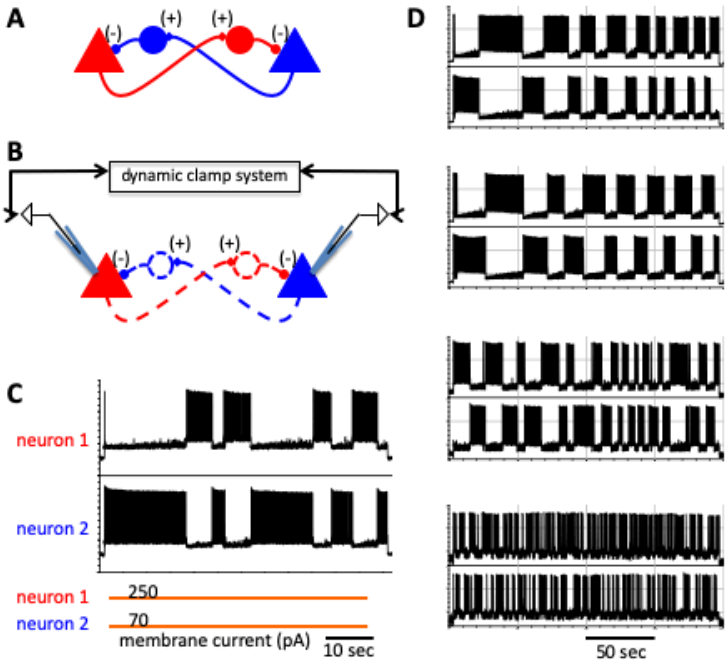

Figure 1. A. Mutual inhibition circuit. Triangle: pyramidal neurons. Circle: inhibitory neurons. B. The connections between the two pyramidal cells were established by dynamic clamp system. C. Injection of depolarization currents evoked bi-stable activities. D. Increase of noise (from top to bottom) caused increase of reversals.

Disclosures: **N. Kogo:** None. **F.B. Kern:** None. **T. Nowotny:** None. **T. Aihara:** None. **R. Van Ee:** None. **R. Van Wezel:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.08

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Discovery Grant (Hopkins)
Science of Learning Grant (Hopkins)

Title: A dilating representation of time minimizing TDRL's valuation error explains observed temporal decision making

Authors: T. MARTON[1], ***M. G. HUSSAIN SHULER**[2];
[1]Neurosci., [2]Neuroscience, Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: By what neural mechanisms do animals represent the passage of time, learn temporal patterns, and decide how to spend time? Is temporal decision-making consistent with algorithms hypothesized from other domains? How do these representations relate to evolutionary pressure to maximize reward accumulation? We investigated how evaluations assigned by temporal difference reinforcement learning (TDRL) relate to decisions about how to spend time. We derive the general solution for how to optimize reward accumulation and prove that memoryless TDRL evaluations (infinite sums of exponentially discounted future rewards) systematically fail to achieve this optimization. However, this failure can be best mitigated by representing time using a time-dilating state space, wherein the amount of time spent in a subsequent state increases by a precise proportion. TDRL applied to a time-dilating state space explains the diverse suboptimalities observed over decades of investigating how animals decide to spend time. In particular, this compromise between memoryless exponential discounting and reward rate optimization preserves optimal forgo behavior, creates a suboptimal bias toward sooner-smaller rewards in mutually exclusive choices, and leads to a suboptimal unwillingness to abandon pursuits that deliver rewards after an uncertain amount of time (sunk cost). Thus, TDRL applied to a precisely time-dilating state space provides 1) the first general mechanistically descriptive explanation of temporal decision making, 2) a normative rationalization for the neural representation of time, and 3) support for the TDRL decision-making framework in the time domain. Temporal decision making can consequently be understood as a near future-biased misestimation of reward rate and opportunity cost, a representation of the infinite future within a finite horizon time, and the representation of the time spent outside an upcoming option as a smaller apparent time inside this horizon time. We present a novel behavioral paradigm validating TDRL's near-future bias.

Disclosures: T. Marton: None. **M.G. Hussain Shuler:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.09

Topic: I.06. Computation/ Modeling/ and Simulation

Support: 4R00MH099654

Title: The primary visual cortex as a window into canonical cortical computations: Prediction and temporal representations in evoked visual responses

Authors: *J. P. GAVORNIK;
Boston Univ., Boston, MA

Abstract: The primary visual cortex is well known for its ability to respond to simple features of the visual environment. Less recognized is its ability to learn and utilize the spatial and temporal structure of experienced visual stimulation patterns. Indeed, recent studies have shown that reward expectation, movement, auditory inputs, attention, and visual experience can all modify evoked activity patterns in V1 though it remains unclear why. A possible explanation for the scope of observations is the idea that cortical circuits, including V1, implement a form of predictive coding that integrates temporal context with current inputs. This talk will focus on how temporal pattern recognition, occurring at multiple time scales and via a variety of mechanisms, supports the hypothesis that predictive coding is a canonical function of cortical circuits that can be studied mechanistically in the early visual system. I will discuss evidence that spatiotemporal coding occurs in V1 over a wide range of time scales to support predictive representations of temporal expectation, conditional probability, and both first- and higher-order sequential relationships.

Disclosures: J.P. Gavornik: None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.10

Topic: I.06. Computation/ Modeling/ and Simulation

Support: MOST Grant 107-2218-E-007-033-
MOST Grant 107-2813-C-007-085-B

Title: Multi-functional microcircuits: Diverse dynamics in small recurrent networks

Authors: *P.-H. LIU, A. J. WHITE, C.-C. LO;
Inst. of Syst. Neurosci., Natl. Tsing Hua Univ., Hsinchu, Taiwan

Abstract: Biological mechanisms are often found to operate in an optimized fashion, maximizing computational abilities while minimizing physical substrates. This can be accomplished if the network is flexible, and current literature supports two complementary explanations for flexibility. First, networks may be flexible in terms of *circuit components*, which means that networks can selectively recruit subcircuits. A study has shown statistically that highly recurrent connections allow subcircuit motifs to act as multifunctional units [1]. Second, networks can be flexible in terms of *circuit parameters*, which means the specific intrinsic properties of neurons allows selective control over which computation a motif performs at any given time. An example is the stomatogastric nervous system of lobsters and crabs, which changes its oscillation properties when given neuromodulatory inputs [2].
Since the more vast a motif's functional repertoire, the more possible functions it can perform, we ask the question: *what type of network exhibits both flexibilities and has the widest functional repertoire?* We used a statistical approach to argue that ***recurrent inhibition*** is one of the key features that expands the functional repertoire of networks. Specifically, we found that recurrent excitation allows working memory, and recurrent inhibition allows decisions and logic like operations. Therefore, we study a type of highly recurrent neural circuits we called CRIREL (Coupled Recurrent Inhibition and Recurrent Excitation Loop). We used a reduced model along with bifurcation theory to investigate different functional operations, and found that CRIRELs are near a 2-cusp bifurcation, which gives rise to functions such as input differentiation, toggling, switching and memory. We then relaxed several assumptions in our model to examine CRIRELs in the context of central pattern generators, and again found many different computations depending on both the intrinsic inputs and extrinsic parameters of the circuit.
[1] O. Sporns and R. Kotter. Motifs in Brain Networks. PLoS Biol, 2, 2004.
[2] T. O'Leary et al. Cell Types, Network Homeostasis, and Pathological Compensation from a Biologically Plausible Ion Channel Expression Model. Neuron, 82, 2015.

Disclosures: P. Liu: None. **A.J. White:** None. **C. Lo:** None.

Nanosymposium

728. Modeling Biological Neural Networks

Location: Room S103

Time: Wednesday, October 23, 2019, 1:00 PM - 3:45 PM

Presentation Number: 728.11

Topic: I.06. Computation/ Modeling/ and Simulation

Support: MOST Grant 107-2218-E-007-033
The Higher Education Sprout Project funded by the Ministry of Science and Technology and Ministry of Education in Taiwan

Title: Multi-functional microcircuits: Robust, flexible control of functionality in small recurrent networks

Authors: *C. LO, **A. J. WHITE**, P.-H. LIU;
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Abstract: One of the most intriguing properties of neural circuits is their flexibility. This flexibility extends far beyond the ability to learn, but includes the ability to use learned procedures to respond to novel situations. It has been well demonstrated that various neural circuits are capable of performing multiple functions depending on the input from the environment, or external input from other brain regions. This ability to switch a neural circuit's operation, simply by changing the external input, has potential application in neuromorphic engineering. Here, we systematically studied flexibility of neural networks by building computational models of small neural circuit motifs. These motifs are found to be common across many different species[1]. We discovered a 4-neuron motif we called Coupled Recurrent Inhibition and Recurrent Excitation Loops (CRIRELs), and found that this particular 4-neuron motif had a large functional repertoire. Upon further investigation, we discovered that CRIREL networks could change their operational type, depending only on the external input into the circuit. This gives the CRIREL circuit the ability to perform a vast array of different operations, including decisions capable of distinguishing between inputs in both magnitude and timing. Perhaps most surprising, we found that CRIRELs can perform eight different digital-like logic-gate operations, using both magnitude or timing as the analog representation of "digital" ones and zeros. Most importantly, we could flexibly switch the circuits logical operation by simply changing the external input into the circuit. We used bifurcation analysis and computer simulations to show that CRIREL's vast flexibility is due to a 2-cusp bifurcation[2]. Furthermore, the circuit's functional flexibility is robust in the presence of thermal and signal noise. Finally, as proof of concept, we show that the biologically inspired circuit motif can be used in a simulated neuromorphic artificial intelligence network to solve logical puzzle game 1A2B (also called bulls-and-cows).
[1] Sporns O, and Kotter R (2004) Motifs in Brain Networks. *PLoS Biol.* 2(11): e369. [2] Hoppensteadt F, Izhikevich E (1999) Weakly Connected Neural Network, Applied Mathematical Sciences. New York, NY: Springer New York

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